The Journal of Laboratory and Clinical Medicine

VOL. 21 MARCH, 1936 NO. 6

CLINICAL AND EXPERIMENTAL

THE NATURE OF RHEUMATIC FEVER*

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IN BEGINNING this symposium it would be well to define the nature of the disease under discussion. This will be attempted so far as contemporary knowledge permits, for it should be recognized that until the etiology is conclusively demonstrated, and specific diagnostic measures are available, most discussions must, of necessity, consist in reviewing theories that knit together current observations.

CLINICAL CHARACTERISTICS

The clinical manifestations of a disease often give a clue concerning its nature, particularly when a given pattern is followed closely enough to permit clear differentiation from not too distantly related conditions. This, upon first glance, would seem to apply to rheumatic fever, and especially to that type formerly known as acute articular rheumatism, with migratory polyarthritis, pyrexia, toxemia, and cardiac symptoms as prominent features. Many variations from this, so-called, typical picture exist; in fact they are sufficiently numerous apparently to comprise the majority of cases encountered in a large general clinic where both children and adults are treated. Monosymptomatic manifestations, such as cardiac insufficiency or chorea may predominate, and the accompanying signs of mild infection, with undernutrition, slight fever, low grade leucocytosis, accelerated erythrocyte sedimentation rate and altered electrocardiograms, may require careful documenting before the rheumatic nature of the disturbance can

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Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

be determined. In fact, the symptomatology may be so obscure that the pathologist's verdict, derived from microscopic examinations, must be the deciding factor.

Temporal variations are equally outstanding. On the one hand, we may see polyarthritis, fever, and toxicity of short duration; the patient recovers and is apparently free from any further rheumatism for the remainder of his life. On the other hand, one encounters a patient with low grade fever, progressive carditis, occasional congestive failure, continued slight leucocytosis, and increased erythrocyte sedimentation rate lasting for years, until finally acute cardiac failure drops the curtain on a life of chronic invalidism. Again, persistent arthritis may be so marked that the physician is in doubt as to whether he is dealing with a case of acute arthritis deformans or of subacute rheumatic fever. First attacks of chorea may be typical, while subsequent recurrences are not infrequently manifestations of habit spasms. Subcutaneous rheumatic nodules are sometimes the chief signs in a person who considers himself to be in perfect health; and how frequently does the cardiologist encounter full-blown mitral stenosis in patients who deny previous rheumatic manifestations, or does the pathologist find Aschoff bodies in the heart of a subject whose clinical history is likewise free from rheumatic stigmas? A realization of the foregoing possibilities makes the experienced clinician cautious when facing a combination of symptoms that have many of the characteristics of rheumatism and yet may possibly be induced by other infections.

One should also recall the tendency for manifestations to recur, especially during childhood, while after puberty this tendency decreases. Puberty, indeed, seems to constitute an important and critical stage in the life of the rheumatic youth. If, because of previous damage, his heart has undergone marked hypertrophy and is unable to meet the demands of rapid bodily growth, ensuing failure soon terminates the picture. If, on the other hand, the child has sufficient reserve to pass this critical period, he will probably live through succeeding years with distinctly fewer rheumatic relapses than he suffered before the age of puberty. The possible relationship between immunity, or resistance, to rheumatism and the action of sex hormones is worthy of more careful study. In passing, one might mention the apparent connection between certain phases of the menstrual cycle and the appearance of rheumatic relapses seen in some women; it occasionally is observed over periods of many months.

The question of the nature of rheumatic relapses is, as yet, unanswered. Are they the result of introduction of fresh infectious material into a susceptible subject, such as we see in erysipelas; are they due to an altered reactivity of tissues so conditioned that slight insults of various types lead to a peculiar mode of response; or are they manifestations of prolonged residence of some infectious agent in the rheumatic subject with periods of almost complete immunity followed by episodes of diminished resistance, comparable to the relapses one sees in syphilis or malaria? Even in patients who appear to be having a continued infection one encounters phenomena indicating alternate cycles of attempts at recovery followed by periods of lowered resistance.

NATURE OF THE HISTOPATHOLOGIC CHANGES

The two active inflammatory responses to injury, viz., exudation and proliferation, are prominent features of the rheumatic processes. The former is illustrated in and about an acutely swollen joint, the latter in the subcutaneous nodule, or in the myocardial Aschoff body. While exudative and proliferative are convenient descriptive terms to apply to different pathologic pictures, they do not represent mutually exclusive processes, and proliferation often exists in the presence of a rheumatic exudate. Both are responses to injury: the exudate, consisting of plasma, or of synovial fluid and wandering cells, is apparently earlier and more evanescent; the proliferate appears later and is more lasting.

McEwen's[1] studies indicate that the proliferated cells are distinctly different from the epithelioid cells encountered in tuberculosis or from those in syphilitic lesions. They are apparently nonphagocytic, and are probably very primitive forms arising from resting mesenchymal cells; although it is possible that at times they may derive from endothelial elements. Their peculiar architectural arrangement in the form of submiliary nodules is claimed by many pathologists to be specific for this disease; other observers regard their presence merely as evidence of a response to injury; and these two schools of thought apparently cannot be reconciled. The Aschoff body, when fully developed, may present a highly characteristic picture; but often cellular arrangements are such that their true character is not apparent unless compared with the, so-called, specific granuloma.

Possibly even more important for an understanding of the pathogenesis of this disease is the altered intercellular mesenchymal ground substance. The collagen fibers show evidence of injury, varying from simple focal edema to fibrinoid swelling and focal necrosis. According to Klinge[2] this precedes proliferation of the primitive cells; indeed, he thinks that this proliferation is the direct response to alterations in the mesenchymal ground substance. What induces these changes is a matter of conjecture; and were it definitely known we possibly might be much closer to a definite understanding of the etiology of this disease. Klinge thinks that it is a manifestation of tissue hyperergy, for he could easily demonstrate fibrinoid swelling in the tissues of rabbits repeatedly injected with foreign protein; and possibly upon this basis one could postulate that the injurious substance was formed by a union of antibody and antigen, presumably of bacterial origin. Fibrinoid swelling, on the other hand, can be induced by bacteria or bacterial toxins, and has also been described in the tissues of noninfected scorbutic animals.[3, 4] Its occurrence, therefore, cannot be definitely attributed to any one type of noxious agent. So far as we know, it has not been induced by filtrable viruses. According to Rivers,[5] all viruses apparently attack primarily either the nucleus or cytoplasm of cells, and the inflammatory reaction is secondary to this cellular injury. We cannot regard the ground substance as cytoplasmic in nature, but rather as an excretory product of the mesenchymal cells; it has more of a supporting than an active metabolic function. If we are correct in assuming that filtrable viruses attack only the active cell bodies or nuclei, it would appear that some other factor was responsible for the focal injury so characteristic of the rheumatic process. On

the other hand, there may be primary points of attack by viruses as yet unrecognized, and if this should be the case, rheumatic fever might be included in this new category.*

STREPTOCOCCI AND RHEUMATIC FEVER

That streptococci may play an important rôle in the causation of rheumatic fever has been the subject of discussion for many years, and recently the possible relationship of hemolytic streptococci has been specially stressed. To review this subject completely would be too time-consuming; hence only the more salient points will be discussed. The long recorded relationship between prodromal tonsillitis or severe nasopharyngitis and rheumatic fever is a matter of common experience. This is especially obvious in adults suffering from their first attack or in those free from the disease for long periods. Following the initial upper respiratory infection there is an apparent quiescent period of a few days to four weeks, the so-called latent period, before the characteristic rheumatic syndrome appears. Unfortunately, careful study of patients during this period is usually impracticable; and in most instances, where carried out, the subjects have been youthful patients in convalescent homes, who have only recently recovered from an attack of rheumatism. Coburn and Pauli[6, 7, 8] have studied nurses, some previously rheumatic and some not. Because tonsillitis is usually associated with heavy hemolytic streptococcal infection, and also because severe nasopharyngitis is often similarly characterized, it has been quite generally assumed that the rheumatic sequellae to these respiratory infections have had these microorganisms as the immediate causative agents. Several observers have shown that precipitins[8] against certain chemical fractions of hemolytic streptococci and also that antistreptolysins[9, 10] and antistreptofibrinolysins[11] appear in the blood about the time of onset of rheumatic symptoms. It has, therefore, been tacitly, if not actively, assumed that some of these antibodies may possibly play a pathogenic rôle in this disease; such an argument is particularly cogent if it is postulated that the pathogenesis rests in part on an allergic basis. Todd[9] originally demonstrated that a large proportion of patients with active rheumatic fever have, what he considered, abnormal concentrations of antistreptolysins in their serums, and therefore concluded that this was highly suggestive evidence of recent hemolytic streptococcal infection. Coburn and Pauli[8] concurred with these conclusions, but reported that the appearance of precipitins against streptococcal proteins was more characteristic of active rheumatic infection than was the occurrence of antistreptolysins.† Most observers agree that high antistreptolysin titers are characteristic of hemolytic streptococcal infections rather than of rheumatic fever. Our own experience,[12] as well as that of others, indicates that precipitins against streptococcal

*Andrewes has recently described a variant of the rabbit fibroma virus of Shope, which variant induces chiefly inflammatory lesions in rabbits. The evolution of these virus-induced inflammatory lesions has not been minutely described; but Andrewes' observations apparently afford an exception to the general rule laid down by Rivers that invasion and injury of cells by virus precedes inflammation. (Andrewes, C. H.: Viruses in Relation to the Aetiology of Tumours, Lancet 2: 63 and 117, 1934; Faulkner, G. H., and Andrewes, C. H.: Propagation of a Strain of Rabbit Fibroma Virus in Tissue-Culture, Brit. J. Exper. Path. 16: 271, 1935.)

†Subsequent to the preparation of the present review Coburn and Pauli (Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. II. Observations on an Epidemic of Influenza followed by Hemolytic Streptococcus Infection in a Rheumatic Colony, J. Exper. Med. 62: 137, 1935) recorded an outbreak of rheumatic relapses in a group of rheumatic girls in whom the symptoms and antistreptolysin curves ran closely parallel.

proteins are usually demonstrable following streptococcal infections unaccompanied by rheumatism. We are, therefore, forced to the conclusion that the presence of all antistreptococcal antibodies thus far described is characteristic of hemolytic streptococcal infection rather than of the rheumatic state, and that none of these antibodies are peculiar, either qualitatively or quantitatively, to this rheumatic state.

Wilson and her coworkers[13, 14, 15] have, indeed, recently concluded that their data, dealing with the isolation of hemolytic streptococci from the throats of rheumatic and nonrheumatic children and with the occurrence of antistreptolysins in their serums, indicate no relationship at all between streptococcal infections and rheumatic fever. Data so apparently out of accord with the experience of most other investigators merit some comment, because neglect of prophylactic precautions based upon a streptococcal theory of etiology (at least contributory) may lead to serious consequences for rheumatic patients. Admitting that hemolytic streptococci were recovered from the throats of most of their patients, one would like to know the kind of streptococci. What were the colonial, pathogenic, or toxicogenic characters of the streptococci recovered? To what serologic group[16, 17] did they belong? So far as we now know members of Group A and possibly of Group F comprise the majority of strains probably pathogenic for man. There is reason to believe that human beings often carry members of other groups in their throats with impunity; and, in fact, according to the findings of Lancefield and Hare,[17] strains not belonging to Group A can live in such highly vulnerable areas as the birth canals of parturient women without inducing disease. Furthermore, these non-Group A strains do not induce antistreptolysins against the soluble hemolysins produced in broth by Group A streptococci.[18] If then, for sake of illustration, a patient were carrying Group B strains in his throat this would have no influence on the antistreptolysin content of his serum when tested by the usual methods. As carried out by these investigators, the identification of hemolytic streptococci by simple inspection of growths of mixed cultures on blood agar plates is exceedingly difficult; and obviously this technic gives no idea of the serologic group to which the streptococci belonged. Granting, however, that the cocci recovered were all members of Group A, this is no assurance that they would induce a rise in the antistreptolysin curve in the carrier's serum, for in our experience roughly 20 per cent of patients definitely infected with proved Group A streptococci failed to show a significant rise in the antistreptolysin in their serums. The carrying of pathogenic streptococci deep in the tonsillar crypts or in the lymphatic glands might escape detection in cultures made from pharyngeal swabbings; but such deeply situated streptococci might easily induce the formation of antistreptolysins in high titers and still the causal relationship be unobservable. Finally, the failure of Wilson's group of children to show the usual seasonal late winter and early spring rise in rheumatic relapses is different from the experience of most observers in New York City. This unusual happening suggests that possibly some prophylactic measures or other factors may have interfered with the customary course of events. It explains, in part, how difficult it is to compare these observations with those of others.

Coburn and Pauli's data and conclusions[6, 7, 8] are the direct antithesis of those just discussed. These observers carefully investigated the streptococci isolated, and identified at least six different types belonging to Group A. Dr. Lancefield has proved the existence of at least ten different serologic types belonging to Group A among the strains isolated from our rheumatic patients; and in Griffith's[19] recent paper fifteen different types from rheumatic individuals were recorded as identified by the slide agglutination technic. As in all of the works just cited the same types were recovered from nonrheumatic patients with streptococcal infections, it seems obvious that none of these strains carry any unique rheumatism-inducing properties.

Coburn and Pauli's[6] numerical data are worthy of citation. During a three-year period, in one-third of their rheumatic subjects there were neither hemolytic streptococcal infections nor rheumatic recrudescences, while in another third the order of events was characterized by an appearance of streptococci in the throat prior to a rheumatic attack. Among the remaining third, one-sixth had relapses unpreceded by hemolytic streptococcal infections, one-fourth had many hemolytic streptococci in the throat without a return of rheumatism, and in the remainder no definite relationship between the two phenomena could be demonstrated. These data, which indicate that although the relationship between streptococcal infection and rheumatism is highly suggestive of having a causal character, it is not by any means absolute.* †

Schlesinger, Signy and Payne[20] could demonstrate precipitins against certain chemical fractions of hemolytic streptococci in only one-half of their rheumatic children. These authors state that when these antibodies were present they appeared to be related to a complicating streptococcal infection rather than to the rheumatic syndrome, for many patients with typical rheumatic symptoms, but without a recent history of streptococcal infection, failed to develop precipitins. Our own studies[12] of antibodies in the serums of patients taken repeatedly during the course of an attack have failed to show any constant relationship between severity of symptoms and the presence of precipitins against either the "C" (carbohydrate) or "P" (nucleoprotein) fractions of Group A hemolytic streptococci. In this connection, however, it should be mentioned that in animals, at least, there is not necessarily a direct connection between a hyperergic state of their tissues and the presence of antibacterial antibodies in their serums.[21]

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*These authors have very recently stated that although there is strong evidence indicating the importance of infection with hemolytic streptococcus in initiating rheumatic activity, it is their opinion that this is not the only factor underlying the development of the rheumatic state. (Studies on the Immune Response of the Rheumatic Subject and Its Relationship to the Activity of The Rheumatic Process. III. Observations on the Reactions of a Rheumatic Group to an Epidemic Infection with Hemolytic Streptococcus of a Single Type, J. Exper. Med. 62: 159, 1935.)

†*Note added at time of proof reading:* Very recently these observers noted that patients having streptococcal infections followed by rheumatic recrudescences yielded strains of Group A hemolytic streptococci that were strong erythrogenic toxin and streptolysin producers while from another group of patients infected with streptococci but without rheumatic sequelae the strains of cocci isolated had neither the strong toxin nor hemolysin producing power. They feel, therefore, that the capacity of a given strain to produce certain poisons, together with the tendency of the patient to react in a peculiar manner to the infecting strain, are the requisite factors in the final rheumatic reaction. Their most recently expressed hypothesis appears to border closely on the allergic viewpoint discussed below.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. IV. Characteristics of Strains of Hemolytic Streptococcus, Effective and Non-Effective in Initiating Rheumatic Activity, J. Clin. Investigation 14: 755, 1935. Coburn, A. F., and Pauli, R. H.: Same series. VI. The Significance of the Rise of Antistreptolysin Level in the Development of Rheumatic Activity, J. Clin. Investigation 14: 769. Coburn, A. F., and Pauli, R. H.: Same series. VII. Splenectomy in Relation to the Development of Rheumatic Activity, J. Clin. Investigation 14: 783, 1935.

RHEUMATIC FEVER AND AN ALLERGIC STATE

Much attention has been paid in recent years to the relationship between allergy (better hyperergy), and rheumatic fever. Because the tests have been largely made with the products of streptococci, thought to have some causative relationship to the disease, we shall confine our discussion largely to this phase of the subject. Rheumatic patients have a marked degree of hypersensitiveness to streptococcal proteins or vaccines when introduced either intracutaneously or intravenously.[22, 23, 24, 25, 26] Several sets of statistics indicate that this is higher than in any other group of diseases. With one notable exception, patients with recent streptococcal infections show a similar heightened sensitivity; this exception is subacute streptococcal endocarditis,[26] where the reactivity might be designated as immune hypoergic, for indeed these patients show a high degree of resistance to introduction of living streptococci into their tissues. Rabbits subjected to repeated focal infections with streptococci of low virulence develop a state of hyperergy somewhat comparable to that seen in many rheumatic patients.[27, 28] Animals immunized intravenously, on the other hand, show a state of hypoergy, also called immune allergy, similar to that of patients with subacute bacterial endocarditis.[29] On the basis of these observations we postulated[30] that the differences in the tissue reactivity of patients with rheumatic fever and of those with subacute bacterial endocarditis could be explained by differences in their "ergic" states. Subsequent work has shown that while the immune state in rabbits is rather closely related to the microorganisms with which the animal has been treated, the induced hyperergic state is very broad, both in respect of the manner in which it can be induced, and in the substances with which it may be detected; in other words, an animal made hypersensitive to a given strain of streptococci is also hypersensitive to distantly related strains, and even to irritating substances nonprotein in nature, and to physical traumatic insults. Of even greater interest is the observation that an animal may be immune to one type of streptococci and still show hyperergic manifestations when tested with some distantly related types.[31] Numerous examples of this so-called allergic irritability[32] might be cited, for we are learning that some allergic states are not necessarily so specific in all of their manifestations as once was thought to be the case.[33]

These observations may have a direct bearing in rheumatic fever, for they may explain why such a high proportion of rheumatic patients have marked sensitivity to streptococcal products even though other signs of streptococcal infection are absent. Part of this increased sensitivity may be a manifestation of allergic irritability. This is suggested by the findings of Duckett Jones and Mote[34] that rheumatic patients show a high degree of sensitivity to intracutaneous injections of rabbit serum. Our[35] experience in confirming those observations has led us to the conception that rheumatic patients are unusually sensitive to many different injurious agents. Wilson's observation[15] that her rheumatic patients were more subject to colds than a control group of a similar social status, might be interpreted in a similar manner: an altered state of reactivity of the tissues of these patients possibly rendered them more easily vulnerable to slight infections. If this conception is eventually confirmed, it

gives a point of attack in trying to learn how the hypersensitive condition may be successfully removed. We still feel that all of the possible relationships between hyperergy and rheumatism have not been fully explored.

POSSIBLE FILTRABLE VIRUS ETIOLOGY

The failure of the previously discussed factors to explain completely and satisfactorily the pathogenesis of rheumatic fever has led many observers to the opinion that the disease is due to an undiscovered filtrable virus. Gräff,[36] in Germany, has actively advanced this point of view for years, and Aschoff and Fahr and their followers have shown a tendency to agree with him, in opposition to Klinge's allergic theory.

We have not been unmindful of the validity of this hypothesis, and during the past fifteen years have tested it in numerous ways. Large numbers of the various species of laboratory animals have been injected with the following materials derived from patients with active rheumatic fever: blood, plasma, arthritic, pleural and pericardial exudates, cerebrospinal fluid, emulsions of subcutaneous nodules obtained at biopsy and of rheumatic tissues obtained postmortem; nasopharyngeal exudates that had been obtained by washing the areas with Ringer's solution and also absorbed on cotton plugs that had been introduced into the nares of the patient and then transferred directly to the noses of monkeys. We have, in addition, employed culture media set up in different ways that have proved useful in growing known filtrable viruses. These materials have been injected intravenously, intraperitoneally, intracerebrally, intraarticularly, and subcutaneously; and in some instances we have used animals previously or concomitantly conditioned with streptococcal infections or immunizations. Detailed recital of these experiments would be superfluous in this place. Suffice it to say that aside from discovering, or helping to discover, some new diseases of laboratory animals, the results of these tests have been largely negative. Other workers have been equally unsuccessful in transmitting typical rheumatic fever to animals. The most obvious explanations of these failures are either that a virus was not present in the material used for attempted inoculation, or that the animals employed were not susceptible.

Very recently Schlesinger, Signy and Amies[37] have reported the obtaining from pericardial and pleural fluid of small particles that resemble the elementary bodies found in vaccinia, varicella, psittacosis, and some other virus-induced diseases. These elementary-like bodies were obtained by high-speed centrifugalization of exudates obtained from rheumatic subjects postmortem. When resuspended in formolised saline they were specifically agglutinated in the serum of ten rheumatic patients out of thirty-six tested. Patients yielding these agglutinating serums were in the active subacute or chronic stage of the disease; but the serums of patients with quiescent rheumatism were nonagglutinating; neither were those of patients with a number of other diseases.*

This interesting report contains the first positive evidence suggesting that a virus may have an etiologic relationship to rheumatic fever. It is noteworthy

*Very recently Coles has reported the observation of "virus bodies" in Giemsa stained films of pericardial and arthritic exudates from patients with rheumatic fever, and also in 25 out of 50 control pericardial fluids. No immunologic studies are recorded. Lancet 2: 125, 1935.

that antibodies were demonstrated *only* in serum from patients with *active disease*.

In this connection attention may be directed to the fact that the demonstration of antibodies, or rather the occurrence of what appears to be an antigen-antibody reaction, does not necessarily prove that either the antibody or the substance with which it reacts has an etiologic relationship with the diseased conditions under which they occur. For example: Tillett and Francis[38] demonstrated precipitins against the "C" substance of pneumococci in the serums of our patients during the acute febrile phases of rheumatic fever as well as in that of patients with lobar pneumonia, and with generalized staphylococcal infections. The high agglutinating capacity of the serums from patients with typhus fever for *Bacillus proteus* X-19 might also be recalled; but typhus is due to a member of the Rickettsia group of microorganisms.* Hughes[39] has shown that serums taken from monkeys recently recovered from severe yellow fever contain a precipitin capable of reacting with a precipitinogen which occurs in the blood of monkeys acutely ill with yellow fever. He definitely proved that this precipitinogen is not the virus of yellow fever, but that it appears to be associated with a protein of the albumin fraction, and is entirely independent of the protective antibody resulting from the infection. A similar precipitin, reacting with the precipitinogen in the blood of monkeys, was found in the serum of human beings recently recovered from severe yellow fever infection. In patients with infectious mononucleosis Paul and Bunnell[40] detected antibodies resembling what they described as heterophile antibodies. Recently Bailey and Raffel[41] have shown that these hemolysins and agglutinins for sheep and ox red blood cells are not true heterophile or Forssman antibodies, but are probably the specific response to an antigen having a factor in common with a thermostabile component of these erythrocytes, a certain strain of *B. Welchii* and possibly horse kidney.

In only one of these instances, involving bacteria, Rickettsia, filtrable virus, and unknown infectious agent, respectively, has it been shown that the antigen-antibody reaction involves part of a specific etiologic agent. Of extreme interest is the demonstration[39] that the tissues of an animal with yellow fever may become so altered that they act as true antigens and stimulate in that same animal the production of antibodies which have specific diagnostic significance, but no direct etiologic bearing. These examples are cited not in an effort to detract from the importance of the observations of Schlesinger and his coworkers, but to indicate the necessity for caution in accepting the evidence presented. These authors, moreover, state that their results simply tend to confirm the hypothesis that a virus may play an etiologic rôle, and suggest that if it does have this function it is only partly responsible for the disease manifestations, in which streptococci may act as the activating agents.

*Castaneda definitely established that there is an antigenic fraction of carbohydrate nature common to both the *Bacillus proteus* X-19 and the Rickettsia causing typhus fever. This is extractable from cultures of *Bacillus proteus* X-19 in the so-called X form, which gives precipitin reactions with both anti-Proteus X-19 serum and with the serum of patients who have had typhus fever as well as with that of horses hyper-immunized with Rickettsia.

The antigenic relationship between Proteus X-19 and *Typhus rickettsia:* 1. A Study of the Weil-Felix Reaction, J. Exper. Med. **58:** 55, 1933. 2. A Study of the Common Antigenic Factor, Ibid **60:** 119, 1934. 3. A Study of the Antigenic Composition of Extracts of Bacillus Proteus X-19, Ibid. **62:** 289, 1935.

The synergic rôle of infectious agents in inducing diseases should, indeed, be kept in mind. The best established example of such a phenomenon is the combined action of a virus and a bacillus in bringing out the active symptoms of swine influenza.[42] The virus of herpes labialis is carried by many a person for years with comparative impunity; but let him contract some other infection, the blisters promptly appear; sunburn or hyperthermic therapy have similar activating effects on this virus; and certain phases of the menstrual cycle are regularly accompanied by the appearance of labial vesicles in some women. Herpes labialis is the best example of a virus-induced disease in which the infectious agent remains in the subject's body for long periods; although many students of this general class of diseases claim that persistence of viruses in the body is a characteristic phenomenon.

The assumption that a virus is etiologically significant in rheumatic fever, but requires some synergic influence for its activation would explain a number of previously observed features of the disease. While streptococcal infections apparently remain the most frequent precursors of an attack, infections such as measles or other exanthemas have been noted to play a similar rôle. We have seen an attack ushered in by antismallpox vaccination, and also other attacks apparently induced by such injuries as a sprained ankle or a bruised wrist. Bland and Duckett Jones[43] have reported that a febrile reaction following the intravenous injection of typhoid vaccine may have an effect similar to that of tonsillitis in setting off a rheumatic relapse, and have observed similar relapses following accidents and operations. The activating relationship of the menstrual cycle has already been mentioned; the parallism with herpes is obvious. Whether allergic irritability may result from virus infection is, as yet, unknown; and whether allergic states, induced by bacterial infections, are specially suitable for the development of some virus diseases must also be decided by future investigations.

In any event there is much evidence indicating that streptococcal infections must be seriously considered both in investigating the nature of rheumatic fever, and in its prevention and treatment. The devastating effect of some streptococcal epidemics in groups of rheumatic patients has been convincingly demonstrated.[44, 45, 46] So far as we have been able to learn from carefully compiled statistics, severe pharyngitis or tonsillitis of apparent hemolytic streptococcal origin is liable to be followed by rheumatic relapses in 50 to 60 per cent of previously rheumatic subjects, while similar upper respiratory infections in nonrheumatic subjects are followed by rheumatic symptoms in less than 10 per cent of instances. These data indicate the importance of protecting the rheumatic subject from these infections; and doubtless the great difficulty in affording this type of protection to the dispensary and ward class of our population, when compared with persons in better economic circumstances, explains, in part, the relatively greater frequency of rheumatic fever among the former group. That good hygienic environments alone do not insure protection from this disease is illustrated by recent investigations in England, where hemolytic streptococcal epidemics among boys in boarding schools were followed by numerous cases of rheumatic fever, just as they are observed among children of the working classes.[47] While upon first glance the placing of rheumatic children in

a tropical environment, where they do not suffer from severe streptococcal infection, would appear to offer useful prophylactic conditions, it is obvious that such extensive traveling and dislocation of family life that this would entail is out of the question for most persons suffering from this disease. It appears, therefore, most important to devise and investigate other means whereby streptococcal infections may be rendered less devastating in rheumatic subjects.

SUMMARY

Rheumatic fever presents protean manifestations, which, when few in number, often make it difficult to distinguish the disease from closely related conditions; hence it is impossible to characterize the malady too accurately. The histopathologic picture, while presenting the well-recognized manifestations of inflammation, has certain peculiar features, chief of which are damage to the mesenchymal ground substance by some noxious agent the nature of which has not been definitely established; this damage is followed by hyperplasia and multiplication of primitive cells that often assume a definite architectural form. Inflammatory features are seen early in the rheumatic lesion in contrast to the initial cellular injury followed by the signs of inflammation usually seen in virus-induced diseases. The tissue of rheumatic patients appears to be unusually vulnerable to several injurious agents, and especially to substances contained in or derived from streptococci. Possibly this state of hypervulnerability, or allergic irritability, makes the tissues susceptible to the action of a hypothetical specific virus; on the other hand, the state of allergic irritability may be the result of prolonged action of such a virus, and the immediate attack may be merely set off by a bacterial infection or other traumatic insult. While much investigation remains to establish firmly and to correlate many of the phenomena discussed, the following working hypothesis remains to guide prophylaxis: It appears advisable to protect the rheumatic subject from certain bacterial infections as well as from other injurious and depressing influences if he is to be spared the repeated attacks of a disease that eventually lead to permanent cardiac disability, for repeated or recurring infections usually exert a more deleterious influence than does the initial attack.

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(For discussion see page 573.)

THE NATURAL HISTORY OF CHILDHOOD RHEUMATISM IN MINNESOTA*

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SINCE 1922 I have been in constant attendance at the Lymanhurst Heart Clinic to which the Minneapolis school physicians refer all children who present signs of cardiac disease. To this clinic, too, the school nurses have been instructed to send immediately on their return to school, all pupils who report their absence as having been due to an attack of rheumatism or chorea as well as all children who come to them complaining of leg pains. In 1926 Dowling School, a special school for orthopedic cripples, was opened to cardiac cripples and during the past nine years I have referred to this school 250 children suffering from heart disease. This group has been examined each week during the school year. Because this work has been carried on with the cooperation of the well-organized medical department of the school system, it has been possible to observe these rheumatic patients at the earliest opportunity and excellent follow-up work has also been possible. This study was undertaken to present the natural history of childhood rheumatism in this locality and to estimate the expected number of recurrences in a group of rheumatic children followed over a sufficient number of years. These control data are necessary in order to determine the efficacy of any type of specific therapy which might be tried in the future.

SUMMARY OF CASES STUDIED

Between 1922 and 1935, 1,868 patients have been examined at Lymanhurst (Table I). Of this number 160 had congenital heart disease, 27 extrasystolic arrhythmia, 23 neurocirculatory asthenia, 677 were found to have no heart

Table I

Summary of Cases Examined at Lymanhurst Heart Clinic
1922-1935

Congenital heart disease		160
Extrasystolic arrhythmia		27
Neurocirculatory asthenia		23
No heart disease		677
Nonpathologic murmur		241
Rheumatics		713
1. Potential	405	
2. Rheumatic heart disease	308	
No diagnosis		27
Total		1,868

*From the Lymanhurst School Heart Clinic and Convalescent Cardiac Home.

Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

disease, 241 presented murmurs which were considered nonpathologic in nature. There were 713 patients who gave a history of rheumatism and of this number 308 had valvular heart disease while 405 were considered as cases of potential cardiac disease. In 27 cases no diagnosis was made.

SEASONAL INCIDENCE

As has been pointed out by a number of investigators there is a distinct seasonal variation in childhood rheumatism. In Minneapolis, as shown by

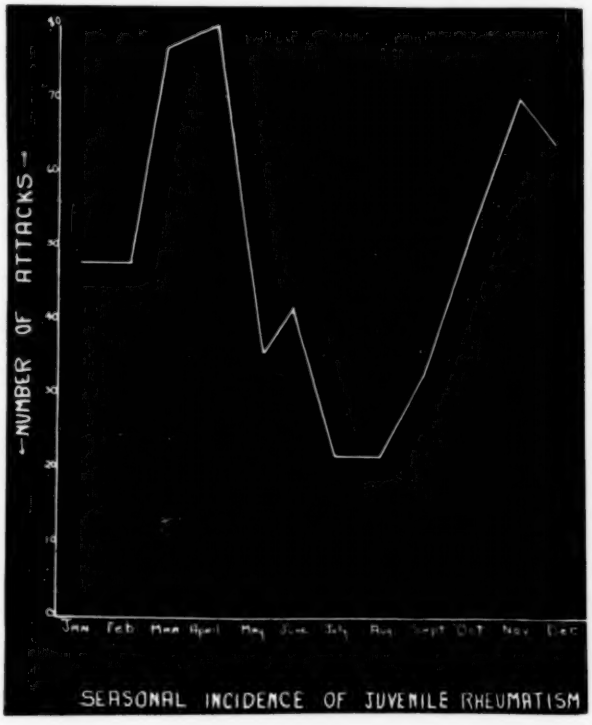

Chart 1.

Chart 1, there is a marked increase in the number of cases in the early spring and late fall. During the summer months rheumatic fever is at its lowest ebb. Other cities in the same geographic location have similar but not exactly the same seasonal variations in rheumatic incidence (Chart 2). It will be noted that the seasonal incidence in London, Philadelphia, and New York is practically the same as that in Minneapolis. In Scotland, however, the peak of incidence is in the fall months of October and November with no spring rise. The cause of this seasonal variation is not altogether clear. The seasonal increase in upper respiratory infections, and dietary deficiencies which are more prone to occur at the end of a long winter, have most often been suggested as possible reasons.

AGE INCIDENCE

Examination of our material indicates as shown by Chart 3 that the onset of childhood rheumatism most commonly occurs between the ages of five and six. This is a somewhat earlier peak of age incidence than is given by most other clinics and is explained by the fact that we have the opportunity of

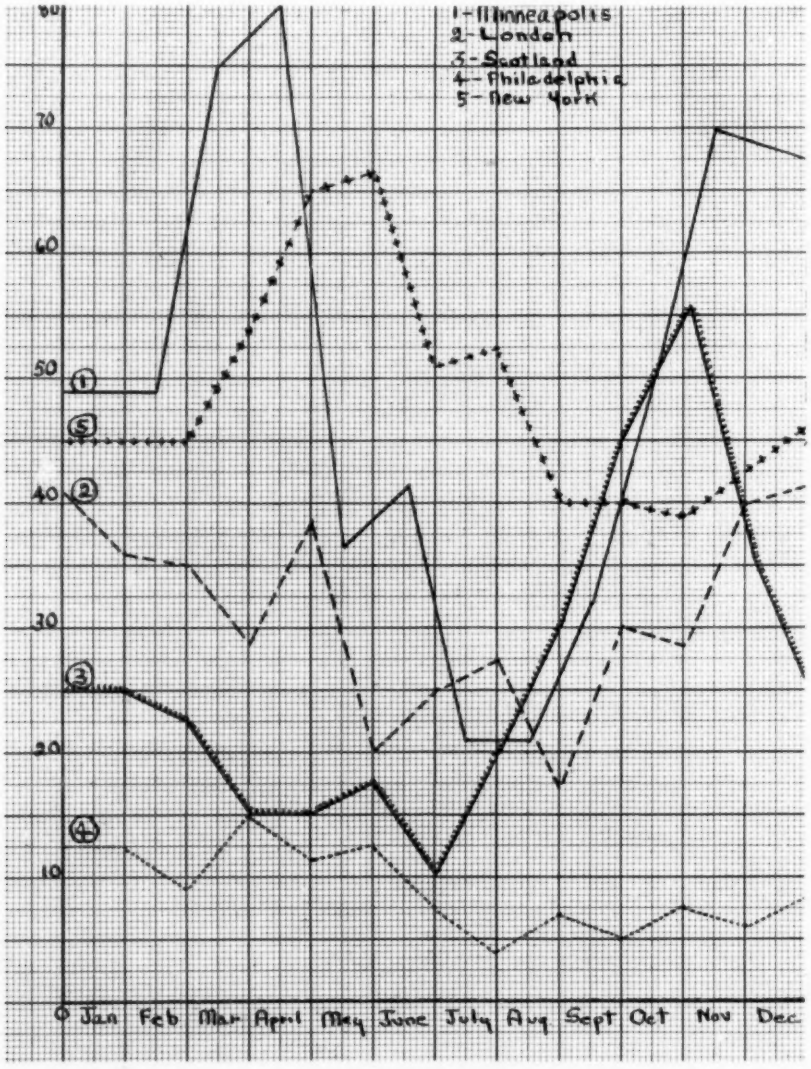

Chart 2.

examining most of our patients at the very onset of the disease. A number of patients have been observed who developed rheumatism during the first few years of life.

FAMILIAL TENDENCY

It has long been known that rheumatic fever is a markedly familial disease. Because of the importance of this phase of the problem our cases were studied

in this regard. During the year 1933 and 1934 all patients who reported to the clinic were questioned carefully concerning family history. Only the parents and siblings were included and care was taken to include in our data only cases which could be considered as childhood rheumatism. During this period 370 children were examined. Of this number, as shown in Table II, 201 gave a history of rheumatic disease, 120 of these patients already had rheumatic heart disease while 81 were potential cases, 67 had congenital heart disease, 44 nonpathologic murmur, 5 neurocirculatory asthenia, 6 extrasystolic arrhythmia, and 47 were found to have no heart disease. Of the 201 children

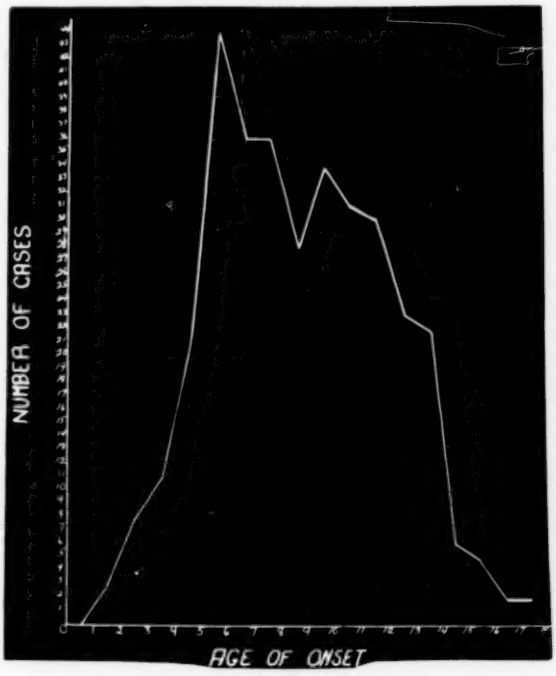

Chart 3.

who gave a history of rheumatism, 94 other members of their families gave a positive rheumatic history an incidence of 46.7 per cent, while among the 169 patients who gave a negative rheumatic history, 25 or 14.7 per cent of the other members of their families gave a positive history, indicating that the family tendency among the rheumatic children was three times as great as among the nonrheumatic control group. These figures do not give the complete picture of familial tendency in childhood rheumatism. It is not uncommon to find two or more members of the same family suffering from rheumatic fever at the same time. It has been suggested that rheumatic fever is a mildly contagious disease and a number of so-called epidemics have been described. Discovery of the etiology of this disease will eventually explain the marked familial tendency.

TYPES OF ONSET

In recent years a good deal has been written concerning the importance of allergy in rheumatism. It has been pointed out by a number of investi-

TABLE II

FAMILY TENDENCY IN JUVENILE RHEUMATISM COMPARED WITH FAMILY TENDENCY IN NON-RHEUMATIC CHILDREN

DIAGNOSIS	CASES	TOTAL NUMBER OF CASES	FAMILY INCIDENCE	PERCENTAGE
Rheumatic heart disease	120			
Potential heart disease	81	201	94	46.7
Congenital heart disease	67			
Nonpathologic murmur	44			
Neurocirculatory asthenia	5			
Extrasystolic arrythmia	6			
No heart disease	47	169	25	14.7
Total number of cases examined 1933-1934	370			

gators that the great majority of children who develop rheumatic fever have a sore throat or upper respiratory infection a week or two before the rheumatism begins. The usual history, according to these investigators, is that the child develops the upper respiratory infection, apparently recovers, and then a week or two later suddenly develops rheumatism. The quiescent phase is explained as the period of developing sensitivity to the upper respiratory infection. During this past year all our patients have been studied in regard to the type of onset. Time-consuming careful histories were obtained from the patients and their parents. These children for the most part had recently recovered from an attack of rheumatism so the facts regarding onset were still clear in their minds. It was found (Table III) that of 201 children studied 27 or 13.5 per cent had a cold preceding the onset of rheumatism, 9 or 4.5 per cent had a sore throat, 4 or 2 per cent had pneumonia, 2 or 1 per cent had measles, 12 or 5.9 per cent developed rheumatism while convalescing from scarlet fever, 20 or 9.9 per cent had chorea before the rheumatism began, 9 or 4.5 per cent of the patients had various types of onset, 2 of these had infected fingers, 2 had abscessed ears, while 1 child injured himself on falling off a porch about ten days before the onset of an attack of rheumatic

TABLE III

TYPES OF ONSET OF JUVENILE RHEUMATISM

ONSET PRECEDED BY:	NUMBER	PERCENTAGE
Cold	27	13.5
Sore throat	9	4.5
Pneumonia	4	2.0
Measles	2	1.0
Scarlet fever	12	5.9
Chorea	20	9.9
Other	9	4.5
Gradual onset	90	44.8
Not obtained	28	13.9
Total	201	100.0

fever. However, 90 or 44.8 per cent of this group developed rheumatic fever gradually, with no preceding respiratory or throat infection. In many instances the patients and their parents were under the impression that the first involved joint was due to an injury while playing. A knee or ankle became swollen, this condition remained unchanged for a number of days while the child continued in school until gradually other joints became involved and the patient was forced to bed with a well-developed attack of rheumatic fever. As a result of this study one concludes that rheumatic fever may be preceded by an upper respiratory infection, but the most common type of onset is a gradual one not preceded by any infectious process.

RHEUMATIC AND NONRHEUMATIC LEG PAINS

All investigators concerned with the problem of rheumatic infection in children are troubled considerably by the history of leg pains. It is difficult to determine which of these children complaining of leg pains are suffering from rheumatic infection and are in danger of developing rheumatic heart disease, and which have no rheumatic infection. It has long been taught that all children who complain of leg pains are rheumatic and potential cardiacs. The public especially has been led to believe that such leg pains are of serious moment, they have been informed that there is no such thing as "growing pains" but that these pains are rheumatic in nature. As a result, numerous such children have had their tonsils removed, some have been confined to bed for long periods of time because of "beginning heart disease" and no doubt a good number of them have had convalescent home care. As a result of our experience over the past twelve years, it is our impression that the great majority of children who complain of leg pains are not suffering from rheumatism and are in no danger of developing heart disease. In an attempt to classify children who complain of pains in the extremities, a differential diagnostic table has been worked out (Table IV) based on clinical observation. A group of known rheumatic children attending Dowling School have been studied in regard to the type of leg pains from which they complained, and these findings have been compared with the symptoms presented by children complaining of leg pains only and who have never had rheumatic fever. Known rheumatic children have more or less constant pain in their joints even while they are up and about and are apparently well. They complain mostly during the day, the pain is intensified on motion, there is difficulty in walking and a limp is often noted. These symptoms ordinarily disappear when the patient goes to bed and rarely do these rheumatic children complain during the night. On the other hand, nonrheumatic children complaining of leg pains have most of their difficulty after going to bed; they commonly awake two or three hours after retiring, and the pain is intense enough to cause them to cry. Heat or massage of the muscles usually causes the pain to disappear, and the child is again able to fall asleep. On arising in the morning the nonrheumatic children are free from pain and complain of no stiffness on walking. The rheumatic children, on the other hand, while they do not complain of leg pains during the night have difficulty in walking when first arising and complain of stiffness for an hour or two in the morning. The

rheumatic children while they may also have muscle pain usually point out the maximum point of pain in the joints themselves, while the nonrheumatic group complain mostly of pain in the muscles of the lower extremities and are unable to locate any point of maximum pain. On being asked to locate his pain the nonrheumatic child will run his hand over the entire lower extremity while the rheumatic patient points directly to his knee, ankle, or elbow joint. The nonrheumatic patient rarely has pain in the upper extremities, the rheumatic child almost always complains of difficulty in all four extremities at one time or another. The nonrheumatic child complaining of leg pains is usually in good health and commonly comes from families in better economic circumstances while the known rheumatic child is usually in poor health and comes from poorer families. The rheumatic child presents other signs of rheumatic activity such as low-grade fever, frequent nosebleeds, pallor, unexplained abdominal cramps, and undernourishment. Frequently, examination of the involved joints in the rheumatic children will reveal local increased temperature, no such findings are present in the nonrheumatic group. A large group of patients complaining of leg pains have been observed for a number of years and will be reported at a later date. It can be noted here, however, that this clinical differentiation has worked well in our experience as almost without exception the children considered as nonrheumatic have not developed signs of cardiac disease. The necessity for differentiating the rheumatic from the nonrheumatic child becomes more and more important as our facilities for treating early cases improves. In a short experience in our Convalescent Home at Lymanhurst we have had to face this problem practically. If care is not taken in selection of patients, a good number of

TABLE IV

DIFFERENCES BETWEEN NONRHEUMATIC "GROWING PAINS" AND JOINT PAINS OF SUBACUTE RHEUMATIC FEVER

	NONRHEUMATIC "GROWING PAINS"	JOINT PAINS OF SUBACUTE RHEUMATIC FEVER
Time of pain	Soon after going to bed. Pain gone in morning. No pain on motion.	Worse on arising. Exaggerated on motion. Difficulty in walking, may cause limp. Pain present during most of day, disappears on getting warm in bed.
Location of pain	In muscles of thighs and legs. Child vague in pointing out site of pain.	In joints themselves. Child points directly to knees or ankles. Often complains of pain in joints of upper extremities also.
General health	Usually good	Usually poor
Other signs of rheumatic activity	Usually none	Common, may have frequent nosebleeds, unexplained fever, pallor, abdominal cramps, undernourishment. Evidence of carditis.
Objective findings in joints	None	Often joints are slightly swollen and hot
Family history of juvenile rheumatism	Uncommon	Very common

nonrheumatic children will be admitted to convalescent homes where they do not belong. The differential diagnosis between the rheumatic and nonrheumatic child is not always easy, and it is our impression that this chart based on clinical observations will tend to assist in making this differentiation.

EXPECTANCY OF RECURRENCES

In order to determine whether or not any specific type of treatment is effective in such a chronic infectious process as juvenile rheumatism, it is necessary first to know what may be expected in a group of untreated patients followed over a number of years. The normal expectancy of recurrences in a group of children with rheumatism has therefore been studied. As indicated in Table V of a total number of 342 rheumatic children, 178 or 52.1 per cent were found to have had one attack only, while 164 or 47.9 per cent of these children had recurrent attacks. Of the 164 patients with recurrences it was found that 44 or 26.8 per cent recurred at the end of the first year while a similar number had recurrences after two years, making a total of 88 patients or 53.6 per cent who had recurrences after two years. Twenty-eight or 17.1 per cent of these children recurred at the end of three years, 20 or 12.2 per cent after four years, and 5 or 3.1 per cent after five years, making a total of 141 children or 86 per cent who had recurred at the end of five years. As the result of this study, it is fair to conclude that it will be necessary to

TABLE V

INCIDENCE OF RECURRENCES IN JUVENILE RHEUMATISM

Total number of rheumatic children examined	342
Children with one attack only	178 or 52.1%
Children with recurrent attacks	164 or 47.9%

RECURRENCES WITHIN	NUMBER	PER CENT	TOTAL	PER CENT
1 year	44	26.8	44	26.8
2 years	44	26.8	88	53.6
3 years	28	17.1	116	70.7
4 years	20	12.2	136	82.9
5 years	5	3.1	141	86.0
6 years	8	4.9	149	90.9
7 years	4	2.4	153	93.3
8 years	5	3.1	158	96.4
9 years or more	6	3.6	164	100.0

follow a group of treated rheumatic children a minimum of five years before any definite conclusions can be drawn. In a number of instances reports have occurred in the literature, giving results of treatment with vaccine for two or three years. As indicated by these figures such reports cannot be altogether conclusive until these patients have been followed a minimum of five years. A detailed study has been made of recurrences in our rheumatic children so that we have excellent control material to use for comparison in any group of children treated in the future.

ANALYSIS OF PATIENTS DEAD OF RHEUMATIC DISEASE

Table VI gives a résumé of the findings in the 34 children of our group that are known to be dead. Undoubtedly the follow-up study which we are

now carrying on will discover many more deaths. It will be noted that in nine instances while these patients were known to have died of rheumatic heart disease, no history of rheumatism was obtained, so that the length of illness from the beginning of the rheumatic process to death could not be

TABLE VI

NO.	SEX	AGE AT DEATH	CAUSE	AGE AT FIRST ATTACK	RECURRENCES	TONSILS	X-RAY	DIAGNOSES	FAMILY	TIME ILL	YEAR DIED
1	M	7- 6	R.H.D.			In	+	M.R. + M.S.	–	None	25
2	F	11- 6	R.H.D.			In	++	M.R. – M.S. – A.R.	+	None	27
3	M	17-10	R.H.D.	2-1 (Rh)	1. 6-11 (Ch)	6-7	+++	M.R. + M.S.	+	15-9	29
4	M	15- 1	R.H.D.	9-2 (Ch)		In	++	M.R. + M.S.	+	5-11	25
5	M	12-10	R.H.D.	4-9	1. 5- 7 2. 11- 4	In	None	M.R. + M.S.	–	8-1	25
6	F	17- 5	R.H.D.	9-5	1. 12- 7	9-6	++	M.R. + M.S.	–	8-0	32
7	F	13- 2	S.A.B.E.	9-0	1. 13- 0	5-3	++	M.R. + M.S.	+	4-2	28
8	M	13-11	R.H.D.	10-0	2. 10-11	2-5	+++	A.R. + A.S. + M.R. + M.S.	–	3-11	29
9	F	14- 9	R.H.D.	9-8		3-1	+++	M.R. + M.S.	–	5-1	34
10	M	16-10	R.H.D.	9-6	1. 11- 2	6-3	+++	M.R. + M.S.	–	7-4	34
11	F	9- 7	R.H.D.	4-9 (Ch)	1. 8- 7 (Rh & Ch)	In	+++	M.R. + M.S.	+	4-10	30
12	F	18- 0	R.H.D.			8-6	++	M.R. + M.S.	–	None	34
13	M	12- 1	R.H.D.	7-10 (Rh & Ch)	1. 11-10 (Rh)	In	–	M.R. + M.S.	–	4-3	27
14	F	15-10	R.H.D.			In	+++	M.R. + M.S.	+	None	26
15	F	13- 4	S.A.B.E.	7-0		9-11	–	Potential	–	6-4	32
16	M	15- 2	R.H.D.			7-11	++	M.R. + M.S.	+	None	32
17	F	12- 9	R.H.D.	6-10	1. 7- 7 2. 9- 0 3. 11- 1	9-5	++	M.R. + M.S. + A.R.	+	5-11	32
18	F	20- 1	R.H.D.			Out	+++	M.R. + A.R.	–	None	32
19	M	16- 8	R.H.D.	7-7	1. 9-10 2. 10- 9	11-2	+++	M.R. + A.R. + A.S.	–	9-1	30
20	M	8- 9	S.A.B.E.	4-7	1. 8- 7	8-7	–	M.R. + M.S.	–	4-2	34
21	F	17- 7	R.H.D.	12-9		15-7	+++	M.R. + M.S.	–	4-10	29
22	M	16- 7	S.A.B.E.	13-9		14-0	+++	M.R. + M.S.	–	2-10	29
23	M	15-11	R.H.D.	12-11		10-9	+++	M.R. + M.S.	–	3-0	27
24	M	15- 5	R.H.D.	8-5 (Ch)	1. 10- 6 (Ch)	8-6	+++	M.R. + M.S.	–	7-0	29
25	M	14- 6	R.H.D.	9-6		In	None	M.R. + M.S. + A.R.	–	5-0	27
26	F	14-10	R.H.D.			In	+++	M.R. + M.S.	+	None	30
27	M	11- 1	R.H.D.			8-9	–	M.R. + M.S.	–	None	23
28	F	5- 4	R.H.D.			In	+	M.R.	–	None	27
29	F	13- 8	R.H.D.	10-5	1. 10- 9 2. 13- 7	In	+	M.R.	–	3-3	33
30	F	12- 6	S.A.B.E.	5-11 (Ch)	1. 7-10 2. 8-11 3. 10- 9	6-8	++	M.R. + M.S + A.R.	–	6-7	30
31	M	11- 4	R.H.D.	10-5		8-4	None	M.R. + M.S.	–	0-11	31
32	M	14- 2	R.H.D.	10-10	1. 11- 4 (Ch) 2. 12- 3 3. 14- 1	11-2	++	M.R. + M.S.	–	3-4	29
33	F	16- 2	R.H.D.	9-0		9-4	++	M.R. + M.S.	+	7-2	33
34	F	13- 5	R.H.D.	6-9	1. 12-7 (Rh & Ch)	8-8	+	M.R. + M.S.	+	6-8	33

determined. Five patients with rheumatic heart disease died of subacute bacterial endocarditis. Most of these children had repeated attacks of rheumatic fever and chorea, the great majority of them had greatly enlarged hearts as indicated by x-ray examination. The average number of years that these patients lived after the onset of rheumatism was about six years. Two-thirds of these children who died had had their tonsils removed.

CONCLUSIONS

1. Rheumatic disease in children in Minneapolis is essentially the same as in other centers throughout the world.

2. Rheumatic fever is more prevalent in Minneapolis in the early spring and late fall. During the summer the disease is at its lowest ebb. Similar curves from other large centers are presented.

3. Childhood rheumatism occurs most commonly between five and six years of age.

4. This disease is definitely familial. The familial tendency is three times as great in a rheumatic group as in a nonrheumatic group.

5. Rheumatism in children in a considerable number of instances follows an upper respiratory infection, but most commonly develops slowly with no preceding infectious process.

6. The great majority of children who complain of leg pains are not suffering from rheumatism. A differential diagnostic table based on clinical observations is presented.

7. The normal expectancy of recurrences of rheumatism has been determined. This material is to be used as a control in determining the efficacy of any type of specific treatment which might be tried in the future.

8. An analysis of the findings of 34 children who have died is presented.

DISCUSSION ON PAPER OF DR. H. F. SWIFT, "THE NATURE OF RHEUMATIC FEVER," AND PAPER OF M. J. SHAPIRO, "THE NATURAL HISTORY OF CHILDHOOD RHEUMATISM IN MINNESOTA"

DR. JOHN WYCKOFF, NEW YORK, N. Y.—The very careful study of Dr. Shapiro is one of the many which have built up the clinical picture that Dr. Swift has so ably reviewed. Each such study has added some new knowledge. Of special interest is Dr. Shapiro's study of the various types of pain, especially in the legs of growing children, some of which are probably rheumatic and some of which are not.

About every two or three years we have learned to expect a comprehensive survey of rheumatic fever by Dr. Swift, a master of the subject. He again brings to our attention certain things which we must hold in our minds; the fact that the disease is extremely complex, and that it is very difficult to say clinically what is rheumatic fever and what is not. He has reviewed the later studies on structural change and has discussed the etiology. I wonder how many times Dr. Swift has come to Atlantic City and has had to listen to a new idea on the etiology of rheumatic fever, has had to act in a receptive mood, and not appear bored.

DR. RALPH KINSELLA, ST. LOUIS, MO.—I feel personally much indebted to Dr. Shapiro for discussing the subject of growing pains. He has made a comprehensive contribution to it.

It is difficult to discuss the subject of Dr. Swift's paper, the etiology of rheumatic fever. My experience is limited to that which concerns the relationship of streptococcal infections with rheumatic fever.

Not every infectious disease has the pattern of a simple, unique reaction such as lobar pneumonia has. There are many infections which have more than one phase, and a capacity for two phases is easily seen in many coccal infections. The double pattern was forecast in miniature, so to speak, in the experiment of Dr. Swift in which he observed a primary exudative reaction to the intradermal injection of living streptococci and a secondary proliferative reaction in the same site without any further manipulation of the animal. The proliferative reaction may continue in the animal due to the continued presence of the exciting agent.

There is no experimental infection as similar to a rheumatic infection, as far as topographic arrangement is concerned, as one by *Streptococcus hemolyticus* or non-hemolyticus. It is possible to establish a chronic infection in animals, in the case of dogs, by infecting the heart valve and in the case of rabbits, by infecting the knee joint; one can keep a continued infection in the animal's body in this way. In the course of time there will be developed proliferative lesions throughout the body that assume a topographic and histologic arrangement like acute rheumatic fever. Some believe it to be identical with rheumatic fever. However, I think the two conditions remain sharply separated as yet.

The proliferative stage of rheumatic fever or of any disease, is probably one that depends for its continuance on the continued presence in the body of the exciting agent; in this case not yet discovered. This mechanism of reacting in a proliferative way seems to be easily set off in some subjects and follows quickly upon the injury to cells produced by virus. The studies of Dr. Shapiro invite the thought that probably children have some change in their internal environment, as far as bacterial agents are concerned, which may depend on hereditary factors.

THE RELATIONSHIP BETWEEN RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS*

M. H. Dawson, M.D., and T. Lloyd Tyson, M.D., New York, N. Y.

DURING the past century there existed considerable controversy over the relationship between rheumatic fever and rheumatoid arthritis. Opinion was more or less equally divided into two schools, those who believed that the two were separate and distinct diseases and those who maintained that they were different expressions of the same fundamental process. At the present time the majority of clinicians both in this country and in Europe consider these two clinical entities as distinct diseases having little or no relation to one another. Occasionally, however, the opinion is still expressed that the two are intimately related and possibly different manifestations of the same process. This is particularly true in the German literature where the relation between the two conditions is constantly discussed.

Older Conceptions.—The evolution of opinion regarding the relationship of rheumatic fever and rheumatoid arthritis is of considerable interest. Ballonius,[1] in 1642, seems to have been the first to differentiate between rheumatism and arthritis but it was largely due to the teaching and writings of Haygarth[2] (1805) and Heberden[3] (1810) that the two came to be regarded as separate diseases. Even at this early date, however, contrary opinions were held and, in his excellent description of rheumatoid arthritis, Scudamore[4] (1827) stated that this disease was merely a variety of "chronic rheumatism." During the remainder of the nineteenth century opinion as to the relationship of the two seems to have been more or less evenly divided between the two schools. Among those who believed that they were distinct entities may be mentioned Fuller[5] (1852), Adams[6] (1857), A. B. Garrod[7] (1859), Fagge[8] and Bristowe.[9] Contrary opinions were expressed by Watson[10] (1836), Todd[11] (1843), Hutchinson[12] (1881), Charcot[13] (1881), Sir Dyce Duckworth[14] (1884), Mitchell Bruce[15] (1894), and Hawthorne[16] (1900). Todd, in 1843, stated: "Chronic rheumatism of the joints is clearly traceable to a rheumatic state of the constitution." Duckworth, in 1884, wrote: "The disease (rheumatoid arthritis) is a true form of rheumatism" and "one of the several manifestations of the rheumatic branch of the basic arthritic diathesis." According to Mitchell Bruce, "the two diseases are expressions of one morbid process which differ from each other partly in intensity and partly in the manner of their evolutions." Charcot stated: "There are not two fundamentally distinct diseases to be dealt with as certain authors fancy,

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The Arthritis Clinic of the Presbyterian Hospital is supported by the Faulkner Memorial Fund.

Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

but only two manifestations of one and the same diathetic state." In a monograph entitled "Rheumatism, Rheumatoid Arthritis and Subcutaneous Nodules," Hawthorne (1900) discussed at length the relationship between the two diseases. He concluded that the presence of similar subcutaneous nodules in both rheumatic fever and rheumatoid arthritis indicated an intimate relationship between the two conditions.

Modern Conceptions.—In more recent times there has been a pronounced tendency on the part of American and English clinicians to regard the two as separate and distinct diseases although occasional contrary opinions are still expressed. Thus Clarke[17] (1915) considers the similar geographic distribution of rheumatic fever and rheumatoid arthritis as being indicative of a relationship between the two. Hare[18] (1928) refers to both rheumatic fever and rheumatoid arthritis under the term "rheumatic disease" and states: "I would advance a more catholic outlook upon rheumatic disease, which, in essentials, remains but one of various inflammations of vascular connective tissue." In a report on "The Relation of Orthodox Rheumatic Infection to Multiple Infectious Arthritis" Coates[19] (1930) presents statistics on the incidence of frank rheumatic manifestations in patients with rheumatoid arthritis and in immediate members of their families. While not drawing any definite conclusions he considers that the figures are, to say the least, significant.

In the German and Scandinavian literature a somewhat different opinion prevails. Here the relation of the two diseases is widely discussed and clinicians have found it convenient to divide rheumatoid arthritis into two groups: (1) primary chronic polyarthritis and (2) secondary chronic polyarthritis. The second group comprises those cases which develop as a sequel to rheumatic fever. The recognition of a group of cases intermediate between rheumatic fever and rheumatoid arthritis is very general among German clinicians and a similar point of view is held by the Scandinavians. Freund[20] believes that, in spite of the similarities between the two, they should be separated for clinical purposes. Fischer[21] is of the opinion that the two are intimately related and that such differences as do exist can be attributed to the varying degrees of immunity possessed by the host. He particularly stresses the fact that there are many transitional cases and that it is frequently impossible to separate the two. Kahlmeter[22] states: "In my opinion, therefore, there is a great deal in favor of rheumatic fever and chronic rheumatoid arthritis being due to a pure infection of the same virus and that the different clinical pictures exhibited depend upon differences in the virulence of the infection and upon the different mode of reaction, temporary or constant, of this virus." Klinge and Grzimek,[23] after extensive investigations on the histopathologic changes in the two diseases, conclude that they are one disease process with different phases and with different clinical and anatomic manifestations in each individual phase.

It is apparent from the foregoing résumé that the current tendency in American and English clinical medicine to regard rheumatic fever and rheumatoid arthritis as separate and distinct diseases does not meet with universal favor. In the present communication evidence will be offered in support of the hypothesis that the two diseases are intimately related and possibly

different manifestations of the same fundamental pathologic process. The following phases of the problem will be considered: (1) Familial relationship; (2) geographic distribution; (3) initiating factors; (4) seasonal incidence; (5) age incidence and clinical manifestations in different age periods; (6) pathologic similarities; (7) immunologic findings.

1. *Familial Relationship.*—It is well known that orthodox rheumatic fever exhibits a marked familial tendency. The statistics of different authors vary somewhat but careful studies show that more than one member of the family is affected in between 37 and 50 per cent of cases (Draper and Seegal,[24] Faulkner and White,[25] St. Lawrence[26]). It is somewhat less generally appreciated that rheumatoid arthritis also shows a definite familial incidence. In a recent study of 100 cases in our clinic, an immediate member of the family was similarly affected in 15 instances. Of more significance, however, is the fact that rheumatic fever and rheumatoid arthritis tend to occur in the same families. In a study of the family history of 50 cases of rheumatoid arthritis, Coates[19] found that in 16 cases (32 per cent) an immediate member of the family suffered from rheumatic fever. In our own series of rheumatoid arthritis cases the incidence of proved, orthodox, rheumatic infection in the immediate family was 14 per cent. Although considerably less than Coates' figures this is at least fifteen times greater than normal expectancy. It must therefore be concluded that rheumatic fever and rheumatoid arthritis tend to occur in the same families. This observation may be interpreted in a variety of ways and assumes significance only in connection with the other evidence of a relationship between the two diseases.

2. *Geographic Distribution.*—Evidence is available to show that rheumatic fever is essentially a disease of the temperate zones. Its incidence diminishes the farther one goes south and it is a relatively rare event in the tropics. (Seegal and Seegal,[27] and Coburn.[28]) Complete data on the geographic distribution of rheumatoid arthritis are not available but the reports of certain observers are significant. The statistics collected by Clarke[17] from the British Army and the Colonial Medical Services show the same geographic distribution for rheumatoid arthritis as for rheumatic fever. For example, the records of the Federated Malay States show that of 71,208 patients treated in one year no case of rheumatoid arthritis appears. The Straits Settlement Medical Report for the same year presents an analysis of 113,509 patients treated in various tropical countries from Nyassaland to Singapore and in only one instance is the occurrence of rheumatoid arthritis recorded. Clarke analyzed the government returns for two years in thirteen tropical countries and found that out of 1,000,000 inpatients not one was diagnosed as rheumatoid arthritis. Examination of the medical reports of the United Fruit Company, whose estates are largely located in tropical countries, shows little evidence of the occurrence of rheumatoid arthritis. Finally, the reports of several observers in Porto Rico and Jamaica indicate that both rheumatic fever and rheumatoid arthritis are relatively rare events in those islands.

The similar geographic distribution of rheumatic fever and rheumatoid arthritis is a matter of considerable interest. So far as we are aware the only

other example of a specific disease which is equally rare in the tropics is that of scarlet fever. It is true that the incidence of both diphtheria and poliomyelitis diminishes in southern latitudes but both of these diseases have appeared in epidemic form in the tropics. In any case, as Clarke has stated, "the concurrent absence of both rheumatic fever and rheumatoid arthritis in the tropics contrasts so markedly with their concurrent presence in temperate climates that it has left the impression that there may be a causal connection between the two diseases."

3. *Initiating Factors.*—The relation between infection of the upper respiratory tract and the initiation of the rheumatic process is well established. There is general agreement that the relationship is too constant to be a mere chance occurrence. In rheumatoid arthritis the relation is less clear and there are many who will doubt its importance. Nevertheless, conspicuous examples are from time to time observed in which the disease appears to be undoubtedly ushered in by a preceding attack of tonsillitis or sore throat. In our experience

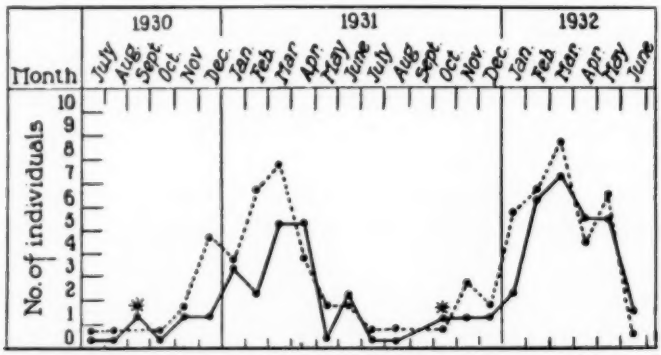
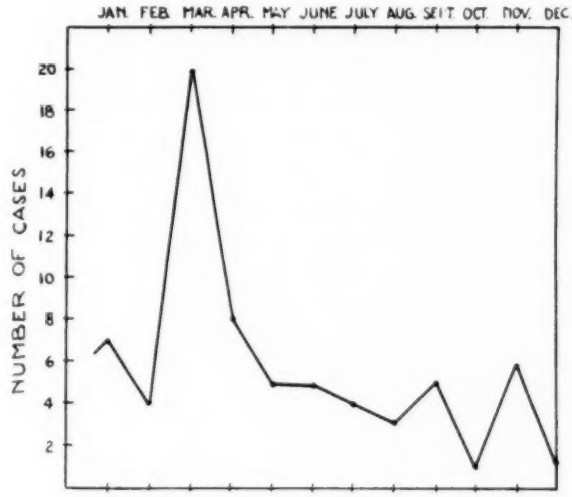


Fig. 1.—Seasonal incidence of hemolytic streptococcus pharyngitis and recrudescences of rheumatism among 165 ambulatory rheumatic subjects in New York City. The peaks occurred during the spring months, and were followed by a rapid rise in the incidence of recrudescences among ambulatory rheumatic subjects. (After Coburn.)
.....indicates hemolytic streptococcus pharyngitis.
————indicates acute rheumatic fever.
*Throat cultures not obtained during September, 1930 and 1931. Patients experienced preceding pharyngitis.

such examples are encountered more frequently than is generally supposed. Approximately 20 per cent of cases give a definite history of such infection and in a further 20 per cent a more equivocal history can be obtained. It is our belief that preceding infection of the upper respiratory tract constitutes one of the most important factors in the initiation of the disease rheumatoid arthritis.

4. *Seasonal Incidence.*—In the United States and Canada rheumatic fever exhibits a definite seasonal incidence, reaching a peak in the month of March. This is true not only for the initial attacks but also for subsequent exacerbations. The seasonal incidence of rheumatic recrudescences together with the seasonal incidence of hemolytic streptococcal pharyngitis is shown in Fig. 1. In such a chronic and insidious disease as rheumatoid arthritis, it is more difficult to speak of a seasonal incidence. However, a careful study of cases in New York City reveals a seasonal incidence which corresponds closely with that of rheumatic fever. The month of onset in a series of 68 cases in which the time of

onset could be accurately determined is shown in Fig. 2. This similarity in the seasonal incidence of the two diseases constitutes a further link in the chain binding the two conditions together.



SEASONAL INCIDENCE OF ONSET OF RHEUMATOID ARTHRITIS

Fig. 2.

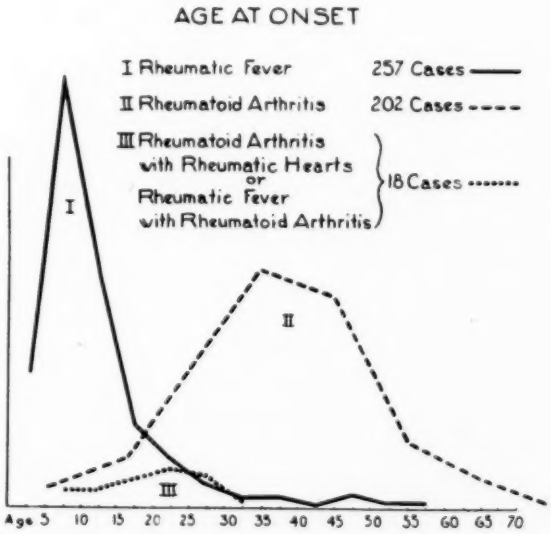

AGE AT ONSET
I Rheumatic Fever 257 Cases
II Rheumatoid Arthritis 202 Cases
III Rheumatoid Arthritis with Rheumatic Hearts or Rheumatic Fever with Rheumatoid Arthritis 18 Cases
I
II
III
Age 5 10 15 20 25 30 35 40 45 50 55 60 65 70

Fig. 3.

5. *Age Incidence and Clinical Manifestations of the Two Diseases in Different Age Periods.*—Rheumatic fever is essentially a disease of childhood while rheumatoid arthritis is predominantly a disease of adult life. The age of onset of 257 cases of rheumatic fever and 202 cases of rheumatoid arthritis is shown in Fig. 3. It will be observed that in nearly 90 per cent of the patients the onset of

rheumatic fever occurs before the age of fifteen while in over 90 per cent of the patients the onset of rheumatoid arthritis occurs after the age of fifteen. More significant, however, is the fact that the clinical manifestations of the two diseases differ widely in different age periods. It is well recognized that rheumatism in childhood presents a different picture from that seen in adult life. As long ago as 1889, Cheadle[29] wrote: "In the rheumatism of early life arthritis is at its minimum; endocarditis, pericarditis, chorea, and subcutaneous nodules at their maximum. As life advances this is gradually reversed; the joint affection becomes prominent, constant and typical of the disease and reaches its maximum; while the other phenomena decline and tend to die out." A summary of the clinical manifestations of rheumatic fever at various age periods is presented in Table I.

TABLE I

CLINICAL MANIFESTATIONS OF RHEUMATIC FEVER AT VARIOUS AGE PERIODS (AFTER COBURN)

INFANCY		CHILDHOOD	
Pancarditis	++++	*Pancarditis*	++++
Vague symptoms	++	Epistaxis	++++
Pallor	++	Vague symptoms	++++
Chorea	+	Erythemas	+++
etc.		Chorea	+++
		Subcut. nodules	++
		Polyarthritis	++
		etc.	
YOUNG ADULT		**ADULT**	
Polyarthritis	++++	*Chronic arthritis*	+++
Epistaxis	++	*Polyarthritis*	+++
Vague symptoms	++	Pancarditis	±
Pancarditis	++	etc.	
Erythemas	+		
Subcut. nodules	+		
Chronic arthritis	+		
etc.			

The clinical picture of rheumatoid arthritis is more constant in various age periods than that of rheumatic fever, but it also shows significant variations. Attention is called to the occurrence of carditis in classical cases of rheumatoid arthritis, a more frequent event than is generally recognized. In our clinic we have observed 22 examples of this condition and, in a series of 100 consecutive cases, 7 were found to have unequivocal signs of rheumatic heart involvement. It is of special significance that the onset of all these cases occurred in the earlier decades of life, in the majority of instances between the ages of fifteen and twenty-five. Reference to Fig. 3 will show that this is the age period intermediate between that of rheumatic fever and rheumatoid arthritis.

In the minds of many observers the occurrence of typical rheumatoid arthritis in children and the undoubted examples of the development of classical rheumatic fever in the later decades of life may constitute a formidable argument against the hypothesis which is here being presented. In this connection, however, attention should be called to certain facts. In the first place, rheumatoid arthritis in children, or Still's disease, is a relatively rare condition. In a six-year period, during which over 800 cases of rheumatoid arthritis have been observed in

our clinic, only 10 patients under twelve years of age have been seen. In the second place, rheumatoid arthritis in children may at times appear as a fulminating infection accompanied by acute joints, high fever, marked leucocytosis and occasionally pericardial involvement. McCrae[30] described two cases in which pericardial effusion was so marked that tapping was necessary. In three of the cases originally described by Still[31] complete synechia of the pericardium was found at autopsy. It is difficult to offer any explanation for the infrequency of endocardial involvement in Still's disease but, by general consent, pericarditis is one of the most characteristic of all the manifestations of orthodox rheumatic infection. With regard to the development of orthodox rheumatic infection late in life attention is directed to two facts. In the first place, such cases are relatively rare. In the second place, it is exceedingly difficult, even impossible, to be certain that a prior infection has not occurred in the earlier decades of life.

Reference has already been made to the occurrence of rheumatic heart involvement in rheumatoid arthritis. Attention is also directed to the fact that chronic joint changes do develop fairly frequently as a sequel to rheumatic fever. In the German and Scandinavian literature it is customary to refer to these cases by the term "secondary chronic polyarthritis." Freund[20] refers to 110 cases in his own experience while Fischer[21] describes 202 cases. While such an incidence suggests that the disease picture in Europe may be somewhat different from that with which we are familiar in this country, examples of this form of rheumatic disease are not infrequently encountered in a large outdoor clinic. The following statistics from Fischer's clinic on the differentiation of "primary chronic joint rheumatism" (rheumatoid arthritis) and "secondary chronic joint rheumatism" are also of interest. He states:

1. The "primary" form shows its maximum two decades later than the "secondary" form.

2. The "primary" form leads more frequently (52 per cent) to ankylosis and deformity than the secondary form (37 per cent).

3. Cardiac involvement occurs much more frequently (65 per cent) in the secondary form than in the primary form (4 per cent).

Finally, brief mention should be made of those cases in which a differential diagnosis of the two conditions cannot be readily made. It is commonly stated that the disease, rheumatic fever, responds to salicylates, is associated with carditis, and leaves no permanent disability of the joints. Rheumatoid arthritis, on the other hand, does not respond to salicylates, is not associated with carditis and almost invariably proceeds to a permanent disability of the joints. It has already been shown that two of these criteria possess only a relative value and reference will now be made to the third differential point, the different effect of salicylates.

In the minds of many the different effect of salicylates constitutes one of the most fundamental distinctions between rheumatic fever and rheumatoid arthritis. It must be pointed out, however, that salicylates have no effect on the course of events in rheumatic fever except on the exudative manifestations and

as antipyretics. They are quite without effect in the proliferative stage of the disease during which cardiac manifestations are so prone to occur. Furthermore, the effect of salicylates is less dramatic in adults than in children and is occasionally quite disappointing. Finally, salicylates are the most universally used of all drugs in the treatment of rheumatoid arthritis, as well as of rheumatic fever, and, while rarely so dramatic in the former condition, their administration is frequently attended by the greatest symptomatic relief.

It will be admitted by all that, among large groups of rheumatic fever and rheumatoid arthritis patients, many borderline cases occur. They are most commonly observed in the late adolescent and early adult years and are more frequently encountered among ambulatory out-patients than among hospital patients. In our own clinic this type of case is not infrequently seen and defies precise classification in spite of all clinical and laboratory examination.

6. *Pathologic Similarities.*—The most convincing evidence of a relationship between rheumatic fever and rheumatoid arthritis is to be found in the pathologic changes. In the present paper reference will be made only to the similarity of the subcutaneous nodules and the vascular lesions. For a detailed study of other histopathologic changes the reader is referred to the work of Klinge and Grzimek.[23]

Subcutaneous nodules constitute one of the most highly characteristic features of rheumatic fever. In 1881 Barlow and Warner[32] wrote: "Such nodules are in themselves indicative of rheumatism." Cheadle[29] stated that the nodules are "absolutely and solely rheumatic" having, so far as he can judge, "no other origin or connection." Osler[33] expressed the opinion that "their presence may be regarded as a positive indication of rheumatism." Hawthorne[16] in 1900 wrote: "The eruption of fibrous tumors in the subcutaneous tissue . . . is a final and unequivocal proclamation in favor of rheumatism." Coombs[34] has recently stated that the subcutaneous nodule is the most "rheumatic" of all the manifestations of orthodox rheumatic infection. Finally, it has been shown in recent years that the nodules exhibit a highly characteristic histologic structure which is strikingly similar to that of the Aschoff body in the myocardium.

One of us has shown elsewhere that subcutaneous nodules, with a highly characteristic histologic structure, are frequently observed in rheumatoid arthritis.[35] Clinically and pathologically these nodules show a remarkable similarity to those which occur in rheumatic fever. Indeed, the evidence suggests that the nodules in the two conditions represent different phases of the same, fundamental, pathologic process and that such differences as do exist are differences of degree and not of kind. Nodules with a similar histologic appearance have not been described in any other disease. Therefore, as Hawthorne has stated, it is impossible to insist upon the appearance of subcutaneous nodules as a conclusive proof of rheumatic fever and, at the same time, to maintain that rheumatic fever and rheumatoid arthritis are not related diseases. Manifestly one or the other conclusion must be abandoned.

Reference has already been made to the occurrence of cardiac involvement in rheumatoid arthritis. Although of relatively rare occurrence this appears to be of the same nature as that which occurs in rheumatic fever. Unfortunately, it is rarely possible to examine the heart pathologically during the acute stages of rheumatoid arthritis. It is, therefore, impossible to express any final opinion as to the exact nature of the changes which take place. However, it is of considerable interest that vascular lesions similar to those which occur in rheumatic fever also occur in the vessels of the subcutaneous nodules in rheumatoid arthritis.[35]

7. *Immunologic Findings.*—Although the etiology of rheumatic fever has not been finally established, a large body of circumstantial evidence has been brought forward by Coburn[28] and others indicating that infection by *Streptococcus hemolyticus* plays a rôle of great importance in the production of the disease. This evidence is, for the most part, based on clinical, bacteriologic and epidemiologic studies. In addition, an important immunologic observation has been made by Todd[36] and by Coburn and Pauli[37] to the effect that the antistreptolysin titer of the serum increases significantly during a rheumatic attack. This evidence suggests that the rheumatic process is initiated by infection with *Streptococcus hemolyticus.*

In rheumatoid arthritis there is comparatively little clinical, bacteriologic, or epidemiologic evidence suggesting that *Streptococcus hemolyticus* is concerned in the production of the disease. There is, however, considerable immunologic evidence of a suggestive nature, although of a different order from that which has been obtained in rheumatic fever. It has been shown that, in the majority of instances, the serums of rheumatoid arthritis patients agglutinate hemolytic streptococci in significantly high titers.[38] Agglutination reactions of a similar nature are not observed in any diseases other than those due to hemolytic streptococcal infection. It has furthermore been shown that precipitins for fractions of hemolytic streptococci can be demonstrated in those serums which possess high agglutinating properties.[39] These findings offer suggestive evidence in support of the conception that infection by *Streptococcus hemolyticus* plays a rôle in the production of the disease.

Finally, reference should be made to the fact that the immunologic evidence suggesting hemolytic streptococcal infection is of a different nature in the two diseases. In rheumatic fever the serums show an increased antistreptolysin content but do not contain agglutinins in significantly high titers. In rheumatoid arthritis serums, on the other hand, significant agglutinins are present but the antistreptolysin content is not elevated, except in early and active cases.

In the present state of knowledge it is difficult to evaluate the significance of these immunologic findings in the two diseases. It is possible that they may represent different responses to infection by the same agent but no final opinion may be expressed until the etiology of both diseases has been definitely established.

DISCUSSION

The relationship between rheumatic fever and rheumatoid arthritis is, at the present time, of greater theoretical than practical importance. For clinical

purposes it is important that the two should be differentiated whenever possible for, in typical cases, each presents its own symptoms, each demands its own therapeutic management and each requires its own prognosis. For theoretical reasons, however, a clearer understanding of the nature of the relationship of the two diseases is of great importance and may contribute much to our knowledge of both conditions.

Evidence has been presented to show that rheumatic fever and rheumatoid arthritis are intimately related and possibly different manifestations of the same pathologic process. Of particular significance is the clinical and anatomical evidence obtained from a study of "atypical" and "borderline" cases. The clinical evidence suggests that the two form a continuous sequence of one disease process with different expressions in each individual phase. These different expressions appear to be in large measure determined by the age of the patient but undoubtedly other factors, such as individual host susceptibility, are also of importance. The pathologic evidence, representing a difference in degree rather than in kind, strongly suggests that the two represent different responses to the same, or closely related, etiologic agents.

A final understanding of the relationship between rheumatic fever and rheumatoid arthritis will not be possible until the etiology of both diseases has been definitely established. At the present time there is a certain amount of evidence suggesting that infection by *Streptococcus hemolyticus* plays a rôle in the production of both diseases. However, this evidence is as yet far from complete and, even if it could be established that both diseases were due to the same agent, it would not prove their identity. The situation would then be analogous to that which exists with syphilis and yaws. Here the etiology of both diseases is definitely known, yet the relationship between the two is still a matter of controversy. It is obviously more difficult, with the knowledge at present available, to arrive at a complete understanding of the relationship between rheumatic fever and rheumatoid arthritis.

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DISCUSSION

DR. CURRIER McEWEN, NEW YORK, N. Y.—A few years ago, at the suggestion of Dr. Swift, we studied supravitally the cells of rheumatic subcutaneous nodules, to obtain further information about the nature of the typical cells of rheumatic granulomas. The appearance of these cells when exposed to Janus green and neutral red was found to be different from that of cells of certain other granulomas. It seemed useful to conduct a similar study of the subcutaneous nodules of rheumatoid arthritis. In nodules from eight such cases we have been able to examine the living cells and have found them in all essentials the same as those of the subcutaneous nodules of rheumatic fever. Similar studies of granulation tissue removed from joints at operation showed the cells to have the same characteristics. This is in marked contrast to syphilitic and tuberculous granulation tissue. Thus it is seen that not only is the general microscopic appearance of the granulomas of rheumatic fever and rheumatoid arthritis similar, but also the individual cells of these lesions are the same. This does not by any means prove the identity of the two diseases, but it is one more link in the chain of evidence connecting the two.

DR. JOHN R. PAUL, NEW HAVEN, CONN.—Drs. Dawson and Tyson deserve credit for emphasizing with such vigor a relationship between these diseases. Many have hinted at their similarity, but few have insisted that they are both the same disease. It seems to be essentially a question of definition. As it is difficult or impossible to define rheumatic fever, it is equally difficult to insist that another disease picture actually is rheumatic fever.

Drs. Dawson and Tyson suggest that the difference between the two conditions is a question of virulence of the organism or of the susceptibility of the host. It seems to me that the susceptibility of the host should be considered first, in that there are certainly few diseases in which the symptomatology is conditioned by age more than it is in rheumatic fever, resembling tuberculosis in that respect. The presence of different types of cases of rheumatic fever and rheumatoid arthritis within the same family is perhaps an example of this age susceptibility. We recently saw a family in which a child of four years developed acute rheumatic carditis, a child of nine, subacute rheumatic fever with joint involvement, and just about the same time the mother developed rheumatoid arthritis.

It is one thing to admit that there is probably a relationship between these two conditions, but it is another thing to have to act upon the suggestion. We have had this decision brought to us very seriously in our work on the epidemiology of rheumatic fever

among families and communities. In certain communities we have been struck by the high incidence of rheumatic fever. We have also found a high incidence of cases of rheumatoid arthritis in these same communities. For our own practical purposes we have, in some instances, almost been forced to consider these two clinical pictures as manifestations of one disease.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—Dr. Dawson has made a good case in favor of the relationship between rheumatic fever and rheumatoid arthritis. However, in following a number of cases of rheumatic fever over a period of years, I have never observed a single patient with rheumatic fever develop chronic arthritis. Many of my patients have reached the period between twenty and thirty years of age when they would be expected to develop rheumatoid arthritis. If these two diseases are closely related it seems to me that I should have observed an occasional case of rheumatic fever develop into rheumatoid arthritis. I have seen four instances when patients in the early teens have developed long-continued swelling about various joints which looked much like rheumatoid arthritis but in each instance the joints did finally clear up completely with no change therein as evidenced by x-ray examination. Those of us who are studying rheumatic fever from its inception should be able to answer this question if we live long enough.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—We have heard much about the age incidence in the development of these diseases, but have possibly neglected another important temporal factor, the period during which the patient may have been exposed to conditions, either infectious or environmental, favorable for the development of the particular type of rheumatism from which he may be suffering. This idea arises from an interesting observation of Dr. Boas a few years ago, that adult Porto Ricans who had recently come to New York from Porto Rico often had the type of rheumatic fever we are accustomed to see in children who have resided in New York all their lives. It is probable that the lack of rheumatic fever in Porto Rico has resulted in these people not developing any resistance to the disease, so that when they suffer their first attack their tissues are in a condition somewhat comparable to that of children.

DR. J. A. KEY, ST. LOUIS, MO.—It is interesting to study two diseases that are so different. I do not know much about rheumatic fever, but I do feel that it is quite dangerous to assume that two diseases are identical or closely related because similar nodules are present in each. Personally, it has been my impression that rheumatoid arthritis was not familial and that hypertrophic arthritis might be familial. I hope that Drs. Dawson and Tyson will continue their studies and later give us a paper on the differences between rheumatoid arthritis and rheumatic fever.

DR. R. L. CECIL, NEW YORK, N. Y.—Dr. Dawson's ideas are intriguing. It has occurred to me, however, that there is one stumblingblock in the way of accepting them, namely, the occurrence of Still's disease in children. If the differences between the two diseases are dependent largely on age, it would be hard to explain Still's disease, a condition now generally looked upon as rheumatoid arthritis in childhood.

DR. DAWSON (closing).—We appreciate that rheumatic fever and rheumatoid arthritis in their classical forms are distinct clinical entities, and we believe that it is important that they should be distinguished clinically. However, we do insist that the two disease pictures overlap and that it is frequently impossible to separate them.

We do not feel that the occurrence of Still's disease, which we regard simply as rheumatoid arthritis in children, constitutes a serious obstacle to our argument. After all, cases of Still's disease are relatively rare and these patients not infrequently show evidence of cardiac involvement, usually pericardial. On the other hand, one occasionally sees cases of orthodox rheumatic fever late in life; but, again, such cases are most unusual compared with the incidence in childhood.

Regarding the development of chronic joint changes following orthodox rheumatic infection, Dr. Shapiro does not encounter them because he is working exclusively with children.

We are dealing with an older group of patients and such cases not infrequently come to our notice. Furthermore, we feel that there may be a difference in the clinical picture of these two diseases in different parts of the world. For example, Freund in Vienna reports 110 cases of "secondary chronic polyarthritis" and Fischer in Germany reports 202 cases in his own personal experience.

A plausible explanation for the different conceptions held by different clinicians regarding the relationship of the two diseases may be found in the type of cases studied. We have primarily been interested in a large group of ambulatory patients. In our material borderline cases are encountered much more frequently than is generally supposed.

GEOGRAPHIC DISTRIBUTION OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN THE UNITED STATES*

E. STERLING NICHOL, M.D., MIAMI, FLA.

WHEN it was suggested that a summary of our knowledge of the regional distribution of rheumatic fever and rheumatic heart disease in this country would be timely, I was reminded of a remark by Poynton under somewhat similar circumstances in England some years ago when he said, "I am in the position of one who has already overwritten himself on the subject (rheumatic fever), and we know that knowledge advances much more slowly than the writing of papers." So it is with apology for repetition that I have gathered together in review the data showing the variable geographic distribution of both rheumatic fever and rheumatic heart disease in the United States. It is hoped that the restatement of these surveys may stimulate others to appraise more accurately the incidence of this disease in their own regions. By way of emphasizing the influence of geographic location on the clinical incidence of rheumatic fever and rheumatic heart disease, my studies on this score in southern Florida are included.

Compilation of hospital statistics from various cities by Faulkner and White[1] and Harrison and Levine[2] in 1924 indicated that the incidence of rheumatic fever is much lower in the southern than in the northern part of the United States. In 1926, Wood, Jones and Kimbrough[3] showed by comparative analysis of hospital records that rheumatic heart disease is half as common in Virginia as in Massachusetts. It was further shown by the collection of hospital data of Seegal and Seegal[4] in 1927 that although the incidence of rheumatic fever anywhere varies with the years, yet for a given period of years the incidence in southern cities is markedly lower than in northern cities of this country. It should be noted that these authors, recognizing that data compiled from questionnaires filled out by hospital record clerks might be inaccurate, cautioned against too much reliance being placed on their rates.

Other studies of the incidence of rheumatic fever or rheumatic heart disease in various localities have been recorded and are included in Tables I and II. In considering this data it is necessary to keep in mind just what concept each author had regarding the inclusiveness of the term "rheumatic fever." In general the condition may be said to include cases with and without arthritis, rheumatic carditis whether acute, subacute or "smouldering," and chorea. Chronic, inactive cases of rheumatic heart disease were not usually classed as rheumatic fever. Any departure from this usage of the term will be noted in the tables, but two instances merit special comment. In 1931 Longcope[5] in discussing the variations in the manifestations of rheumatic

*Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

fever in relation to climate, stated that in Baltimore the incidence of rheumatic fever admissions to adult medical wards of Johns Hopkins Hospital was 1.3 per cent which is equivalent to the rate given for a similar hospital in Boston. This is surprising until one discovers that Longcope counted cases of *quiescent* or *inactive* rheumatic heart disease as examples of rheumatic fever. The discrepancy becomes apparent on comparing the autopsy statistics given by the same author, which indicate that rheumatic heart disease is encountered at autopsy in Baltimore with less than half the frequency found in Boston. This author did emphasize, however, that the arthritic manifestations of rheumatic fever are less outspoken in that locality, compared with cities farther north, and that it is essentially a disease of the heart of a rather insidious type. Likewise in 1933, McLean[6] in computing the admission rate

TABLE I

ADAPTED FROM PUBLISHED DATA REGARDING HOSPITAL INCIDENCE OF RHEUMATIC FEVER IN THE UNITED STATES

LOCATION OF HOSPITAL	LAT. N.°	YEARS INCLUDED	MED. ADM. RATE RH. FEVER OR CHOREA	REPORTED BY
Spokane, Wash.	47	1920-23	3.0	S. & S.‡
Portland, Ore.	45	1920-25	1.2-4.5	S. & S.
Portland, Ore.	45	?	0.1*	Coffen[14]
Boston	42	1914-23	1.85*	H. & L.
Boston	42	1918-22	1.3	F. & W.
Cleveland	41	1920-25	2.0-5.0	S. & S.
Iowa City	41	1923	2.4	F. & W.
Omaha	41	1923	0.7	F. & W.
New York	40	1915-25	2.0-6.0	S. & S.
New York	40	1915-31	0.1-1.8**	Davis[15]
Philadelphia	39	1918-23	0.5-1.2	F. & W.
Baltimore	39	1914-22	0.7*	H. & L.
Baltimore	39	1925-30	1.3†	Longcope[5]
Denver	39	1924-25	1.0-2.1	S. & S.
St. Louis	38	1922-23	0.47	F. & W.
St. Louis	38	1916-23	1.0*	H. & L.
University, Va.	38	1926-32	1.5†	H. W. & D.
San Francisco	37	1920-25	1.2-1.6	S. & S.
San Francisco	37	1919-23	3.75	F. & W.
Norfolk, Va.	36	1926-32	0.15	H. W. & D.
Oklahoma City	35	1922-25	0.0-0.2	S. & S.
Memphis	35	1920-25	0.1-0.5	S. & S.
Los Angeles	34	1921-24	0.44	F. & W.
Augusta, Ga.	33	1918-23	0.08	F. & W.
Birmingham	33	1917-25	0.0-0.5	S. & S.
Birmingham	33	1922-32	1.8†	McLean[6]
San Diego	32	1925	0.45	S. & S.
Charleston	32	1923-25	0.1-0.2	S. & S.
Dallas	32	1919-25	0.0-0.3	S. & S.
New Orleans	29	1915-25	0.1-1.0	S. & S.
New Orleans	29	1916-23	0.3*	H. & L.
Galveston	29	1915-25	0.0-0.2	S. & S.
Galveston	29	1913-23	0.8*	H. & L.
Tampa	27	?	0.4	B. & C.
Miami	25	1930-34	0.13	Nichol§

*Cases of chorea not included.

**Includes *only* cases with arthritis.

†Includes *also* chronic inactive rheumatic heart disease.

§My own figures added for comparison.

‡S. & S., Seegal and Seegal[4]; H. & L., Harrison and Levine[2]; F. & W., Faulkner and White[1]; H.W. & D., Hart, Wood and Daughton[16]; B. & C., Bitzer and Cooke[17].

of rheumatic fever at the Children's Hospital in Birmingham included all instances of *chronic* or *inactive* rheumatic heart disease, with the result that the rate obtained of 1.8 per cent is considerably higher than it would be had the usual clinical concept been followed. There is no doubt, however, that the incidence of rheumatic fever in Birmingham is relatively high compared with some sections of the South, though unfortunately no autopsy statistics were given. McLean also showed the infrequency of arthritis as a manifestation of rheumatic fever in Birmingham and stressed that there, also, rheumatic fever is primarily a disease of the heart.

Another factor possibly detracting from the reliability of the comparative data in Tables I and II is the varying alertness of the attending physicians making the diagnosis of rheumatic fever in each instance, or judging whether a given case of heart disease is of rheumatic etiology. In children in particular it is commonly admitted that the early stage of heart disease is not an easy subject. The variable picture of the rheumatic state has been amply portrayed in clear fashion by Coburn,[7] and in a recent monograph dealing with the etiology of rheumatic heart disease, Paul[8] has stressed the difficulty of making accurate etiologic studies of a disease so variable in its presenting symptoms.

TABLE II

REPORTED FREQUENCY OF RHEUMATIC TYPE OF HEART DISEASE AMONG HOSPITALIZED "CARDIAC" PATIENTS IN VARIOUS CITIES

HOSPITAL LOCATION	LAT. N.°	YEARS	% OF RHEUMATIC HEART DISEASE	REPORTED BY
Portland, Ore.	45	1929	10.1	Coffen[14]
Boston	42	1924	39.8	Wood, et al.[3]
Chicago	41	1932-33	16.7	Flaxman[18]
Salt Lake City	40	1927-29	40.4	Viko[19]
Louisville	38	1928-33	8.0	Simmons[20]
University, Va.	38	1923-26	21.9	Wood, et al.
Washington, D. C.	38	?	6.0	Gaeger and Dunn[21]
Nashville	36	1930-31	10.5	Laws[22]
Galveston	29	1920-26	7.3	Stone and Vanzant[23]
Miami	25	1931-34	19.0*	Nichol

*Only 2 per cent was acquired in Florida. My own figures added for comparison.

In spite of these difficulties, after making allowance for the probable errors in the collected data and the difference in clinical concepts, it seems apparent on reviewing the data, that, on the whole, clinically perceptive rheumatic fever and rheumatic heart disease are much less common in southern than in northern regions of the United States. Nevertheless, a comparison of the frequency with which rheumatic heart disease is encountered at autopsy in various sections of the country obviously should give the most accurate index of the influence of geographic location and climate on the occurrence of rheumatic fever. Some of the autopsy data given by Harrison and Levine[2] and a few other reports of the incidence of rheumatic heart disease found at autopsy in certain regions have been combined in Table III. My own figures for southern Florida have been added for comparison. It is only fair to point out that in some southern cities autopsy statistics may give rise to an

exaggerated notion of the incidence of rheumatic fever, since the winter resort regions are invaded during the winter months by many individuals from the North with rheumatic heart disease, some of whom eventually die while in the South and make up a fair share of cases arriving at necropsy. It will be seen

TABLE III

REPORTED FREQUENCY OF RHEUMATIC HEART DISEASE FOUND AT AUTOPSY IN VARIOUS CITIES

HOSPITAL LOCATION	LAT. N.°	YEARS	% OF RHEUMATIC HEART DISEASE	REPORTED BY
Boston	42	1914-23	4.0	Harrison and Levine[2]
Cincinnati	39	1927-30	3.0	Glazer[24]
Baltimore	39	1925-30	1.6	Longcope[5]
Oklahoma City	35	1919-24	0.0	Harrison and Levine
New Orleans	29	1916-24	0.2	Harrison and Levine
Miami	25	1931-34	4.0*	Nichol (present report)

*Actually only 0.5 per cent if allowance is made for migration of patients.

the available data indicate that the ratio of rheumatic heart disease found at autopsy in southern cities is much less than in northern cities. It has been suggested[9] that since these studies are based on gross pathologic findings, such as the presence of mitral stenosis or rheumatic pericarditis, that further studies should be made including microscopic examination of standard sections of the heart tissues to make sure that some grades of rheumatic carditis have not been overlooked.

INCIDENCE IN SOUTHERN FLORIDA

A more striking portrayal of the way geographic location and climate influence the distribution of rheumatic fever and rheumatic heart disease in this country is seen on comparing my own studies in southern Florida (25° latitude N.) with the figures from Boston (43° latitude N.). Having made further inquiry since my previous reports[10] on this subject, I have combined the data for the five-year period from 1930 to 1934 inclusive, showing the incidence of rheumatic fever and rheumatic heart disease at Jackson Memorial Hospital, Miami, an institution admitting patients of all descriptions. Previously published data for the years prior to 1930 are not included, as it is only since that date that practically all patients admitted to the hospital wards with rheumatic fever or rheumatic heart disease have been examined by the author. It is felt that this close acquaintanceship with the patients making up this data lends considerable weight to its importance, as all questionable instances of rheumatic infection were carefully studied in order properly to classify them.

During the five years there were only 11 cases of rheumatic fever or carditis, acute, subacute or "smouldering," and no cases of chorea, found among 8,287 medical admissions, including children, giving an admission rate of 0.13 per cent (Table IV). This is in sharp contrast to the admission rate during the same period at the Peter Bent Brigham Hospital, Boston, of 1.4 per

cent, as determined by Levine[11] who found 137 cases of rheumatic fever, chorea or carditis, acute or "smouldering," among 9,817 medical admissions. (The incidence would have very likely been even higher if children under twelve years were admitted to this hospital.)

TABLE IV

COMPARISON OF HOSPITAL MEDICAL ADMISSIONS FOR RHEUMATIC FEVER IN BOSTON AND MIAMI DURING 1930-34 INCLUSIVE

HOSPITAL	CITY	NO. MED. ADM.	NO. CASES RH. FEVER, RH. CARDITIS OR CHOREA
Peter Bent Brigham	Boston	9,817	137* or 1.4 %
Jackson Memorial	Miami	8,287	11† or 0.13%

*Twenty-three cases of chorea.
†No chorea; only 3 cases with arthritis.

TABLE V

INCIDENCE OF RHEUMATIC HEART DISEASE IN MIAMI AS DETERMINED FOR THE YEARS 1931-34 INCLUSIVE

NO. "CARDIAC" CASES OF ALL TYPES FROM		NO. CASES WITH RHEUM. HEART DISEASE	NO. CASES RHEUM. HEART DISEASE ACQUIRED WHILE IN MIAMI
Jackson M. Hosp.	561	106 or 19.0%	11 or 2.0%
Office practice	408	68 or 16.6%	2
Total	969	174 or 17.9%	13 or 1.3%

*Part of these cases are included in a previous communication.[10]

In view of this extremely low incidence of active rheumatic infection in Miami, it would be expected that in a series of cardiac patients hospitalized, the number classed as being of rheumatic origin would be correspondingly small. It is seen in Table V, however, that during the years from 1931 to 1934 inclusive there were 106 instances of rheumatic heart disease among 561 patients with cardiac disorders in the hospital. Although the percentage obtained (19.0 per cent) is only half that reported in some northern hospitals, it exceeds the ratio given for some northern points, as was seen in Table II. This discrepancy might indicate that many instances of *active* rheumatic carditis were overlooked in the hospital wards, but a study of the clinical histories of the patients classed as rheumatic heart disease reveals that *all* had acquired their structural cardiac damage before migrating South, except for those described above with *active* rheumatic infection. Thus only 2 per cent approximately of the total group of patients with heart disease should be classed as having rheumatic heart disease originating in Florida.

The frequency with which rheumatic heart disease is encountered in office practice in southern Florida is also illustrated in Table V. Of 408 cardiac patients examined in the period from 1931 to 1934 inclusive, 16.5 per cent or 68 were classed as being of rheumatic etiology, but with *one* exception all had acquired rheumatic disease before leaving the North, and *in* only *one* instance was there clinical evidence of reactivation of a "healed" rheumatic carditis among the 68 patients during their stay in the South. On combining the hospital and office data, it is seen that there were 174 instances of rheumatic heart disease among 969 cardiac patients (17.9 per cent). But only

13 patients or 1.3 per cent of the total group acquired rheumatic heart disease during their life or residence in Florida. In contrast to this, it has been shown by White and Jones[12] that in New England (Boston) among 3,000 patients with heart disease encountered in hospital, clinic, and private practice, 31.9 per cent were classed as being of rheumatic etiology.

On considering the available pathologic data, it was found that among 401 autopsies performed during the past four years at Jackson Memorial Hospital, there were 89 instances in which death was due primarily to heart disease, and of these 16 or 4 per cent gave anatomical evidence of *rheumatic* heart disease. But again on inspecting the clinical histories, it is shown that in fourteen instances the rheumatic pathologic changes had been noted in the North, and that in only two instances was the rheumatic infection acquired in the South. Thus, actually, only 0.5 per cent of the autopsies performed during this period showed rheumatic heart disease originating in Florida.

COMMENT

Many physicians have questioned the actual rareness of rheumatic fever in the South. As to the validity of their doubts for some sections of the South, I cannot vouch, but ten years of observation of the scene in southern Florida has convinced me that as far as this section of the South is concerned even the very mild or smouldering form of rheumatic carditis is quite uncommon while the obvious cases with arthritis or chorea are rare indeed. During the past five years in particular I have watched for the subclinical forms of rheumatic fever, which, it was claimed following my first report, probably escaped clinical notice. In my opinion there is very little ground for the feeling expressed editorially recently by Hench and others,[13] that it might be better to have rheumatic fever in the North, where it is recognized early due to its more acute form, than in the southern states where the diagnosis might be missed, owing to an insidious onset, thus favoring more damage to the heart of the victim, who would go untreated for a longer period. If this were the case a general hospital in southern Florida should provide a far greater number of cases of rheumatic heart disease than it does, as seen above.

SUMMARY

A review of available data indicates that there is a definite inequality in the distribution of rheumatic fever and rheumatic heart disease in the United States, the amount being much less in the southern states. The influence of geographic location on the clinical incidence of rheumatic fever and rheumatic heart disease is emphasized by contrasting the findings in southern Florida and New England. During the past five years, in spite of a careful search for subclinical cases, the admission rate of rheumatic fever, rheumatic carditis or chorea in a general hospital in Miami was only one-tenth the rate in Boston during the same period.

Only 1.3 per cent of "cardiac" patients found in Miami both in hospital and office practice had rheumatic heart disease determined clinically to have been acquired during life or residence in the South, compared to a recent estimate that 31.9 per cent of "cardiac" patients encountered in New England were of rheumatic type.

This clinical evidence of a low incidence of rheumatic fever and rheumatic heart disease in the South is borne out to some extent by the available autopsy statistics, provided that in the figures for southern Florida allowance is made for the migration of patients from the North with previously established structural heart damage of rheumatic type. Further pathologic studies of a more detailed character are required to complete the proof of the influence of climate on the incidence of rheumatic fever.

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DISCUSSION

DR. JOHN R. MOTE, BOSTON, MASS.—This review of the geographic distribution of rheumatic fever in the United States is interesting and of importance not only in noting the incidence of heart disease in general, but also in a consideration of the possible etiology of rheumatic heart disease in particular. The hospital incidence of rheumatic fever or rheumatic heart disease may not indicate the real incidence of the disease in a given locality. This may be true especially in southern areas, where the disease in general is less obvious and less characteristic. In addition to the fact that the incidence of the disease decreases as you go south, medical men, according to their experience, differ in their concept of the disease and its significance, and this in itself may affect the apparent incidence. If the medical man believes it to be a trivial disease, the patient is considered well as soon as the joints are free from pain and is not sent to the hospital; whereas in the North, where the medical man may be more impressed with the importance of the illness, the patient may be hospitalized. Furthermore, the relative education of both local practitioners and of the general population in the use of hospitals will further affect the apparent incidence in different sections of the country. Not only may the above points affect the results in considering the incidence of this disease, but also the living conditions and social set-up in different sections and in different groups within a given section may alter the apparent incidence. Thus, White and Jones in the Massachusetts General Hospital wards found that 54 per cent of the cases with heart disease were rheumatic, while in office practice it was considerably less, and in consultation practice the incidence of rheumatic heart disease was relatively insignificant. It is obvious, therefore, that hospital records may not always indicate the real incidence of the disease.

That the incidence of the disease may vary in the same latitude is indicated by the report of Hart and Wood, who found an incidence of rheumatic fever at the University of Virginia Hospital in 1934 of 0.48 per cent of the total hospital admissions, while in the same year in the same latitude at Norfolk, Virginia, the incidence was 0.15 per cent of total admissions.

There are certain rank discrepancies in the reports from over the world on the occurrence of this disease which require verification. Clark states he has seen no rheumatic fever or mitral disease in the Malay States or in the British Army in Southern India, while Church reports a high incidence of rheumatic fever in Ceylon. Menje reported a high incidence in Tahiti, whereas in the Sansoon Islands a very short distance away in the same latitude there is none. A verification of these and other discrepancies in the literature may throw a considerable amount of light on the possibilities in the etiology of this disease.

During the past five years the House of the Good Samaritan has sent each year a small group of children with rheumatic fever to the St. Francis Hospital in Miami Beach, Florida, in an attempt to evaluate, if possible, the effect of a subtropical climate on the course of the disease. During the first four years twenty-three children were sent. In summary of this study it may be said that recurrences with resulting death do occur in this climate, but in general the patients do better and their recrudescences are shorter lived than in the North. It should be stressed, however, that exacerbations of rheumatic fever do occur in rheumatic patients while they are in Florida.

DR. CURRIER McEWEN, NEW YORK, N. Y.—Assuming that the statement that rheumatic fever does improve in the tropics is correct, is the same true of atrophic arthritis?

DR. JOHN R. PAUL, NEW HAVEN, CONN.—I hope that we may soon begin to get some idea of the general prevalence of rheumatic fever in this country. I doubt if nation-wide data can be satisfactorily obtained from hospital admission lists, but a more satisfactory method is the determination of the prevalence of rheumatic heart disease among school children in different parts of the country.

DR. M. H. DAWSON, NEW YORK, N. Y.—While making rounds in a hospital in Jamaica, B.W.I., Dr. Dochez was shown a case or two recently of rheumatic fever. He remarked that he had understood that rheumatic fever was a very rare disease in the tropics. The attending physician replied, "Oh, no, we see cases from time to time, but there is a very curious thing about them, they all come from up in the hills," where, of course, the climate is not truly tropical.

DR. S. A. LEVINE, BOSTON, MASS.—I would like to comment on the difference in incidence of rheumatic fever in different parts of the country. Physicians down South may call rheumatic fever arthritis and so term it in their records. They say that we in the North see more rheumatic fever. In a large general hospital rheumatic heart disease must be seen if it exists in the community for it is eventually fatal. In a hospital of 200 beds in the course of ten years there will be a certain number of patients die of rheumatic mitral stenosis. At death it will be recognized by the pathologist, no matter what it was called in life. At the Charity Hospital in New Orleans the incidence of mitral stenosis was one-twentieth of that which we found at the Brigham Hospital in Boston. This was conclusive evidence to us that either rheumatic fever was markedly less common in New Orleans than it was in Boston or that rheumatic fever occurring down there does not affect the heart like it does in Boston.

DR. NICHOL (closing).—In reply to Dr. McEwen's question, I have no accurate data on the geographic incidence of atrophic arthritis. From an experience of ten years in southern Florida I would state that a patient with atrophic arthritis does not improve at the same rate that one with rheumatic heart disease does in the same period of time. I was asked to prepare some statistics regarding the incidence of atrophic arthritis, but I did not attempt to do so, because statistics not given from one's own experience have very little value.

No one should overlook Dr. Paul's excellent studies on school children. Three years ago I made a survey of the school children in Miami. The difficulties are almost insurmountable for a "one man job." On comparing 1,500 school children born and reared in Miami with 1,500 school children who had migrated to Miami I found that the incidence of rheumatic heart disease was four times greater in the "migrated" group than in the native group. However, some of those children had been sent to Florida because of a previously established rheumatic disease.

AN OUTLINE OF STUDIES RELATING TO VITAMIN C DEFICIENCY IN RHEUMATIC FEVER*

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IN PREVIOUS reports[1, 2] experimental data have been presented indicating that under the combined influence of vitamin C deficiency and infection guinea pigs developed with considerable frequency, endocardial, myocardial, and articular lesions bearing considerable resemblance to those of rheumatic fever. On the basis of these observations, the concept was advanced that rheumatic fever may be the result of the combined influence of vitamin C deficiency and infection. Further experimental studies have confirmed and extended the original findings. It is the purpose of this communication to review the broad experimental basis for the concept, to consider certain epidemiologic and clinical data bearing on the problem, and finally to summarize the basic pathology of rheumatic fever and relate it to the thesis advanced.

EXPERIMENTAL METHODS

As detail of experimental methods has been previously published,[1, 2] a brief outline will serve for the present communication. Guinea pigs were maintained on a basic diet containing all other food factors but devoid of vitamin C. In different experiments, varying grades of deficiency were maintained by regulating the vitamin C supplement which was given in the form of orange juice. The infecting agents in the majority of instances were hemolytic streptococci derived from spontaneous cervical lymphadenitis, which is a relatively common infection in guinea pigs. This use of natural pathogens for the species in all of the experiments is believed to be of considerable importance. It should be noted that there was definite variability in virulence of different strains of hemolytic streptococci used. The most striking lesions occurred in experiments where the virulence of the organism was great. Infection was transferred by intracutaneous inoculation of pure broth cultures of the organism. This resulted in a localized infection of the skin and regional lymph nodes. Occasionally but not commonly, metastatic abscesses occurred in distant sites. It should be pointed out that almost uniformly the local infection in the deficient animals was more intense, less well localized, and less readily healed, than in the control animals receiving adequate vitamin C supplements. While the most extensive observations have been made with the hemolytic streptococcus as the infecting agent and the most striking lesions have been observed with this organism, a few other bacteria including a gamma type streptococcus, *B. aertrycke,* and *B. bronchosepticus* have been used. Studies with these organisms have not been extensive; however, the occasional development of "rheumatic type" lesions, in which infection with these agents has been superimposed on the scorbutic state, suggests that the bacterial factor is not specific.

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Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

An *active* or *virulent* infection would appear to be of more importance than the exact organism. This phase of the problem, however, requires further study.

EXPERIMENTAL FINDINGS

In each of a rather extensive series of experiments, the effects of the uncomplicated deficiency, the deficiency with superimposed infection, and the infection in the adequately nourished animal were studied. *The various infecting organisms in the presence of adequate nutrition, did not produce rheumatic type lesions.*

Inasmuch as the anatomic changes in the heart and articular tissues have previously been described and illustrated,[1, 2] a brief review of the findings will suffice for the present communication. Subsequent studies have simply confirmed and extended the previous reports.

Heart Valves.—In uncomplicated vitamin C deficiency, atrophic and degenerative changes develop in the collagenous stroma of the heart valves. Rarely mild proliferative reactions accompany this degeneration. In vitamin C deficiency with superimposed infection, lesions of a combined degenerative and proliferative nature develop with considerable frequency. These lesions vary considerably and are sometimes striking in character and bear close resemblance to the early rheumatic endocarditis. Ribbert,[3] Clawson,[4] Poynton and Schlesinger,[5] and others have clearly shown that the rheumatic vegetations develop within the valve substance, due to subendothelial proliferation of cells which is most prominent at the line of closure. Small amounts of true fibrin may merge with the cells in the superficial zone. This is essentially the nature of the experimental lesions as well.

Heart Muscle.—The pathologic changes in the heart muscle are less striking than the valvulitis. However, focal proliferative reactions are not infrequently observed. These may be found beneath the mural endocardium, in the pericardium and in the muscle. Some of the most significant reactions develop near the angle of attachment of the mitral valve. The reason, perhaps, that the lesions occur at this site is that there is here, as in the valve proper, a significant amount of intercellular substance (collagen) subject to undue stress and injury which forms the nidus for the proliferative focus. The connective tissue about the coronary vessel branches in the guinea pig heart is insignificant compared with that in the human heart.

The experimental proliferative foci, although not identical, are considered of a basically similar sort to the Aschoff reaction. The cells surround altered collagen and the nuclear and cytoplasmic character of the reacting cells correspond very closely to those composing the Aschoff body.

The Joints.—An early manifestation of vitamin C deficiency in the guinea pig is an arthropathy characterized by pain and swelling. Certain infections superadded to the deficiency accelerate and augment this arthropathy. The same infections in the presence of adequate nutrition do not affect the joints. Pathologic observations on the joints in rheumatic fever are not abundant. The most exhaustive study of the articular changes in rheumatic fever is afforded by the studies of Klinge,[6] and Klinge and Grzimek.[7] These authors find the lesions to be characterized by "fibrinoid" degeneration and granulom-

atous reactions in the capsular and periarticular tissues, mild hyperplasia of the synovial membrane with "fibrinoid" degeneration in the synovial and subsynovial tissues and the presence of hyaline fibrinous material free in the joint space. It is noteworthy that just such changes occur in the experimental animals.[2]

Much evidence has gradually accrued relating rheumatic fever and atrophic (rheumatoid) arthritis. Klinge and Grzimek[7] hold that although acute or subacute rheumatic fever and atrophic (rheumatoid) arthritis may usually be differentiated, both disease pictures are so intimately related in both joint and general pathology that a "rheumatic" basis may be assigned to both. Dawson and Tyson[8] have recently summarized a rather convincing mass of data indicating a relationship between the two diseases. It is perhaps not without significance that in the experimental studies under consideration, no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic-deforming arthritis. Subacute or chronic vitamin C deficiency in the guinea pig produces a painful deforming arthropathy with manifold similarities to atrophic (rheumatoid) arthritis. These include synovial proliferation, intra-articular pannus formation and periarticular fibrous tissue overgrowth. In certain instances, superimposed infection accelerates and accentuates the pathologic process.[9] The general atrophic changes found in atrophic (rheumatoid) arthritis involving the bony skeleton, muscle, and skin are also observed.

Subcutaneous Nodules.—One feature common to both rheumatic fever and atrophic (rheumatoid) arthritis is the subcutaneous rheumatic nodule. Dawson[10] particularly has drawn attention to this lesion and finds the early pathologic histology in both conditions to be essentially the same. The lesion is characterized by hyaline streaks of fibrin surrounded by a reactive overgrowth of connective tissue cells. At times the fibrin is intimately intermingled with collagen. In the experimental animals, particularly those subjected to the more chronic deficiency, such nodules have been seen about joints with considerable frequency.

SUMMARY

It will be seen then that the concept that vitamin C deficiency may be a contributory factor in the etiology of rheumatic fever lies upon a broad experimental base. With vitamin C deficiency and infection combined lesions comparable to those of rheumatic fever are found not only in the heart valves and muscle, but also in the joints. Subcutaneous nodules serve to complete the pathologic similarity. No claim is made for the *identity* of the experimental lesions to those of the human disease. They are, however, thought to be *fundamentally similar.*

EPIDEMIOLOGIC CONSIDERATIONS

Malnutrition has commonly been observed in rheumatic fever. The geographic distribution, the dominant urban incidence, the high incidence in winter and spring and the frequent familial occurrence, might be explained upon the basis of greater liability to infection. On the other hand, these

features are entirely in accord with the operation of a factor of vitamin C deficiency. One epidemiologic peculiarity that particularly suggests an environmental factor other than infection in the genesis of rheumatic fever is the intimate relationship of the disease to poverty. Glover[11] believes that the true incidence of rheumatic fever in England is directly proportional to the degree of poverty and estimates that the occurrence of acute rheumatism is twenty or even thirty times as great in the poor as in the well-to-do. It would appear to me that a disease with such an amazingly high incidence in poor people could not be explained on the basis of a specific infecting factor or on the basis of recurrent nonspecific infection alone. Some fundamental environmental or nutritional influence would seem to lie in the background.

CLINICAL OBSERVATIONS

During the past eighteen months a clinical approach to the problem has been made in association with Dr. Amos Christie at the University of California Hospital. Dietary studies have indicated in most instances borderline or frankly deficient diets with respect to vitamin C particularly in the winter months. Capillary resistance tests have revealed in general low levels which have risen on institution of diets high in vitamin C. It is of interest that in many cases there has been a decided delay in return of this index toward normal indicating the necessity of time for repair of a vascular injury. We do not feel that a diminished capillary resistance is an entirely reliable index of latent scurvy and its reduction in rheumatic fever cannot be assigned to this factor alone. Excellent weight gains have been recorded. One mild recurrence occurred in a child who repeatedly informed us that she was unable to secure the foods advised. A number of the patients have passed through acute upper respiratory infections without reactivation of the rheumatic process. The patients in our series have not yet been subjected to detailed analysis, and we do not consider the group large enough or the period of observation long enough for conclusion. To date, however, we feel that the study has been encouraging. A recent observation of Faulkner[12] is of considerable interest. He found that rheumatic children showing evidence of active disease almost uniformly gave a reticulated red blood cell response of from 3 to 5 per cent following administration of large doses of vitamin C. To me this suggests a deficiency.

DISCUSSION

I wish to make it entirely clear that the factor of infection in rheumatic fever is in no sense minimized. It appears equally essential in the rheumatic fever-like experimental disease. What the precise infecting agent is, if there is a specific factor in rheumatic fever, is not known. It may be one or many forms of the streptococcus, an unknown bacterium, or a virus. Much evidence points to the importance of the common pathogenic hemolytic streptococci. The mode of action is equally uncertain. It may operate through toxin production, through minimal localization or through an allergic mechanism involving antigen antibody reactions. Epidemiologic data, particularly the social distribution, strongly suggests a conditioning environmental influence. The experimental data implicate vitamin C deficiency.

Essential Pathology of Rheumatic Fever.—Rheumatic fever is a disease fundamentally characterized by injury to connective tissues. Klinge[6] particularly has drawn attention to widespread connective tissue injury. A change which he has called "fibrinoid degeneration" he considers to be the basic lesion of the disease. It seems to me that substances included in this descriptive term "fibrinoid degeneration" are one of the following: (1) Swollen, degenerated or necrotic collagen; (2) hyalinized fibrin; or (3) a combination of the two, that is, fibrin-soaked collagen. Collagen degeneration or necrosis is seen in the valvulitis, the auriculitis and at the center of the Aschoff body. Hyalinized fibrin may be present in any rheumatic lesion. It is usually most prominent in the subcutaneous nodules.

Theory of Mechanism.—A consideration of the fundamental pathology of rheumatic fever and the experimental studies suggest a possible mechanism, operating in the development of the lesions. Vitamin C has been shown by the studies of Höjer[13] and Wolbach and Howe,[14] to be essential for the normal metabolism of connective tissue. In the presence of deficiency, preexisting connective tissue substance undergoes degenerative changes and repair and replacement is either in abeyance or accomplished by an imperfect collagen. As the tensile strength of the finer vascular bed is dependent to a large extent upon the intercellular substances, collagen and reticulum, the deficiency would impair their strength and render them more permeable. If such tissues were further insulted by a factor of infection, it would not seem unlikely that they would suffer to a degree that would not occur in normal tissues. Such a concept would explain the acute necrosis or subacute degeneration of collagen that is a fundamental lesion of rheumatic fever. The increased permeability of small vessels would foster this injury of collagen. If the insult of the infecting factor upon the small vessels were great, blood might escape into the perivascular connective tissues. This would explain the hemorrhagic manifestations commonly encountered in the disease. A lesser injury might allow only the escape of plasma from which fibrin would be deposited. The degenerated collagen, the fibrin or fibrin-soaked collagen would act as a stimulus to repair. The reparative mechanism in the presence of a deficiency and a continued action of the injurious factor of infection would be imperfect and manifest itself by pathologic hyperplasia of surrounding connective tissue cells as seen in the Aschoff reaction.

Existence of Latent Scurvy.—Considerable evidence has accumulated indicating that latent scurvy is probably more frequently present in children than is appreciated. Göthlin[15] using reduced capillary strength as an index of latent scurvy found evidence of vitamin C undernutrition in 18 per cent of school children in the province of Uppland (Sweden) during the months of April and May. Dalldorf,[16] working in New York, similarly using capillary resistance tests as a criterion considers that mild degrees of vitamin C deficiency may constitute a problem of considerable public health importance. If dietary histories can be relied upon, many of the rheumatic children in our series were on suboptional diets, some frankly deficient in vitamin C. A recent survey of food purchases of families on relief in a California city[17] revealed inadequate purchase of vitamin C containing foods in a large number

of cases even though the survey was conducted in a season when these foods were plentiful and available at low prices.

Metabolism of Vitamin C.—The ability of the body to store vitamin C is limited. Even without a dietary source of the vitamin, there is a continued excretion of small amounts in the urine. Factors which may deplete the stores of vitamin C are of great interest and probably of great importance. Our own experience from experimental observations is that certain infections may act in this way. Harde and Benjamin[18] have presented brief experimental evidence that infection may deplete the organic stores of vitamin C. Van Eekelen and Kooy[19] have shown that fatigue may operate in a similar fashion. If acute infection depletes the organic store of vitamin C, it is of great importance to the concept presented. Under such circumstances, a mild degree of deficiency might by infection be rendered significantly severe in a relatively short period of time. Such a mechanism might afford a partial explanation of the latent phase noted by many observers between the acute upper respiratory infection and the clinical onset of rheumatic fever. Practically nothing is known of factors which may hinder or prevent absorption or utilization of vitamin C. In light of our limited knowledge of the metabolism of the vitamin interpretations based on studies of urinary excretion must be made with great caution. Harris and Ray[20] have shown that the normally nourished individual promptly excretes relatively large amounts of vitamin C following a large dose. On the other hand, deficient individuals show a lag in excretion. These observations are of considerable interest but conclusions based upon this type of study must be guarded. This method is obviously only a measure of immediate "saturation" level of the individual and gives no indication of a preexisting deficiency. Further, in the presence of a complicating factor as an infection it is probably not safe to assume that high excretion following test doses of vitamin C is an index of saturation. If infection may deplete the store of vitamin C, the ability of the body to utilize the vitamin may be disturbed.

What may we expect of vitamin C therapy in rheumatic fever? If vitamin C deficiency prepares the soil for an infection to produce the rheumatic injury, it is apparent that the deficiency then is only a contributory influence. If we consider the widespread and frequently severe character of this injury it will be appreciated that repair will require time. Further, it would seem that the reparative mechanism would probably be more or less ineffective during the active phase of injury. In severe cases it would appear that much of the finer vascular bed and connective tissues would need to be rebuilt and that these tissues would be susceptible to injury at any time until the restitution were complete. It will be seen then that we are dealing with something more complex than a simple deficiency. Time for repair would probably vary depending upon the extent and intensity of injury. Following severe cases, a period of months in which the tissues were liberally supplied with vitamin C and freed of injurious influences might be required for reestablishment of normal tissue anatomy and resistance. Naturally certain pathologies, as valvular deformities, would never be anatomically restored. The most that could be achieved would be restoration of tissues to a state in which they could resist

the injurious influence of infection. The ability of vitamin C to do this can only be evaluated on the basis of prolonged clinical observation.

Two approaches to the solution of this problem suggest themselves. First, a preventive type study to determine if optimal vitamin C nutrition over an adequate period of time will prevent susceptible groups from getting rheumatic fever. Likewise, a study of rheumatic children could be instituted to determine if a high vitamin C intake would materially reduce the tendency to recurrence. Particularly in this case should the element of time be carefully considered and judgment of effectiveness withheld until the period of observation had been long. The experimental and other data, which have been outlined clearly, indicate the importance of such a clinical study.

SUMMARY

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection, rests upon a broad experimental basis. In guinea pigs, under this dual influence, lesions comparable to those of rheumatic fever may develop in the heart and joints. The not infrequent occurrence of subcutaneous nodules appears to complete the pathologic similarity. It is of interest that in the experimental work no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic joint disability with pathologic similarities to atrophic (rheumatoid) arthritis. There is much evidence indicating a relationship between the two diseases as seen in man.

Epidemiologic data seem to support the thesis advanced. Particular significance is attached to the abnormally high incidence of rheumatic fever in the poor.

Clinical studies in progress have afforded encouraging data, but are too few, and the period of observation too short to afford a basis for judgment.

Rheumatic fever is a disease fundamentally characterized by widespread injury to collagen. Based upon the experimental studies and pathologic anatomy of rheumatic fever, a theory of mechanism of the development of the rheumatic lesion is advanced.

Our knowledge of the metabolism of vitamin C is in the process of development. Capacity to store the vitamin is limited. Fatigue and certain infections may deplete the organic reserve. Factors which might inhibit absorption or utilization of vitamin C are not known. Urinary excretion studies may serve as an index of the immediate "saturation" level but are not a gauge of preexisting deficiency. The possible influence of infection in modifying the storage and excretion or utilization of vitamin C is not known. For these reasons, data based upon urinary excretion must be interpreted with care.

The question of what we may reasonably expect from vitamin C therapy in rheumatic fever is considered in the light of the fundamental pathology of the disease. Even though vitamin C deficiency may contribute to the development of the rheumatic lesion, it is only one factor. Some influence of infection also operates. In view of this, and the frequently severe injury

accompanying the disease, judgment of the preventive or therapeutic effectiveness of vitamin C administration in rheumatic fever can be based only on prolonged clinical study.

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DISCUSSION

DR. HOMER F. SWIFT, NEW YORK, N. Y.—Dr. Rinehart's report two years ago induced us to repeat it. The concept of synergic action of infection and some other factor is a useful hypothesis. Dr. Schultz, in our laboratory, has been able to confirm practically all of Dr. Rinehart's statements. One must ask, however, whether the experimentally induced lesions are truly rheumatic, or merely exaggerated scorbutic tissue changes. Thinking that the relationship between vitamin C deficiency and rheumatic fever would probably be revealed better in the clinic, Drs. Schultz and Sendroy have studied a group of patients in the Rockefeller Institute Hospital. Their results may be summarized as follows: No significant difference was found in the metabolism of vitamin C in rheumatic and nonrheumatic subjects. Fifty-seven previously rheumatic children were divided into two

groups; one received capsules containing 100 mg. of vitamin C daily in the form of Redoxon, the other a placebo. The relative incidence of mild rheumatic relapses among the patients in these two groups was the same; and three of the first group developed severe rheumatic relapses. Fifteen patients with acute active rheumatic symptoms were given 250 mg. of vitamin C daily without any observably favorable influence.

Although many of the rheumatic patients gave evidence of subnormal concentration of vitamin C at the time of admission to the hospital, others apparently had normal amounts in their bodies. Our clinical studies failed to prove the hypothesis that there was a causal connection between vitamin C deficiency and the symptoms of rheumatic fever. In view of the recently announced discovery of an antiinfectious vitamin in fruit juices, it is possible that studies with pure synthetic vitamin C might have given different results from those obtained by the use of citrous fruit juices.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—During the past year I have carried on studies on possible vitamin C deficiency in rheumatic children. The criteria for a diagnosis of latent or subclinical scurvy are not at all clear. It is impossible to make such a diagnosis on patients on clinical findings alone. My work was carried out in the following manner: The habitual diets of 70 children who were known to have rheumatic fever, and of their families were investigated by a trained dietitian. Thirty-nine of these patients were on a diet which was sufficient in vitamin C content while 31 were on a diet which was definitely insufficient. The capillary resistance of these 70 patients was studied. A full mouth x-ray was taken, as well as an x-ray of a knee and a wrist. The capillary resistance test is not standardized and difficult to interpret. The various writers on this subject have used different methods for determining capillary resistance. Some have used simply the tourniquet for three minutes, others have used the blood pressure machine at 50 mm. for fifteen minutes and still others 80 mm. for three minutes while Dalldorf has used his so-called capillary resistometer which is based on negative pressure and takes only one minute to perform. These various methods were tried and an attempt made to correlate them. We decided to use Dalldorf's method because of its simplicity and reliability. It was noted that of the 39 children who had a sufficient diet 24 or 60.5 per cent had a positive capillary resistance test while 15 or 39.5 per cent were negative; and of the 31 children who were on an insufficient diet 19 or 61.3 per cent had a positive capillary test while 12 or 38.7 per cent had a negative test. This would indicate that there is no correlation, whatsoever, between the capillary resistance test and the deficiency of vitamin C in the diet. The factor of toxicity in these rheumatic children as a cause of the capillary permeability must be considered. One is unable to say whether or not the decrease in capillary resistance is due to toxicity or vitamin C deficiency. This preliminary report would indicate that capillary resistance and vitamin C deficiency are not definitely related.

We based our findings in the teeth on the work done by Westin and Höjer of Sweden. I was unable to show any relationship between vitamin C deficiency as indicated in the study of the diet and the findings in the teeth. Of 39 children on a sufficient diet 15 or 39.5 per cent were positive while 23 or 60.5 per cent were negative for dental changes. Of 31 children on an insufficient diet 12 or 40 per cent had positive findings in the teeth while 18 or 60 per cent had negative findings. In no instances did roentgenograms of the joints show definite evidence of latent scurvy. One meets with considerable difficulty as the roentgen findings in subclinical scurvy are not clear. We did find some unusual changes in the bones in a number of these children but consultation with Dr. Leo Rigler, the head of the x-ray department of our university, failed to establish a diagnosis of scurvy. Some of these films were sent to Dr. Bromer of Philadelphia and he also refused to commit himself on these findings. My preliminary investigations thus suggest that there is no relationship between vitamin C deficiency and juvenile rheumatism.

DR. WILLIAM J. KERR, SAN FRANCISCO, CALIF.—The work of Dr. Rinehart and the original work with Drs. Mettier and Connor have been of great interest. The histologic findings resemble closely those seen in rheumatic fever, and perhaps those in the proliferative type of arthritis. It is not so easy to carry results over to the clinic and say that

deficiency of vitamin C is a factor in the production of rheumatism or that we can immediately control the process by substituting vitamin C.

The work which Dr. Swift and his associates reported last month seems to be quite negative so far as the clinical application of the principle is concerned. But we should be sure that we have studied an adequate number of cases over a period of years before we can be quite certain of the results. We must also be sure that whatever substances we are administering actually enter the body. If these substances are given by mouth, conditions for their proper absorption must be satisfied. If there is any uncertainty about absorption we should give them parenterally. As I recall Dr. Swift's report, vitamin C was given intravenously in some instances. If there are other substances in fruit juices, which may be important factors, we should take them into account in treatment.

Dr. Rinehart and his clinical colleagues expect to continue this study for some time, not only on patients with rheumatic fever but also on those with atrophic arthritis.

DR. JOHN R. MOTE, BOSTON, MASS.—At the House of the Good Samaritan we repeated with minor variations the work of Dr. Rinehart on guinea pigs. Briefly it may be said that the results were essentially the same as those of Dr. Rinehart. The animals which had scurvy with an added streptococcus infection showed the most marked lesions in most instances. In the chronic scurvy controls we found the same type of lesion but of a less severe type. In the group of acute severe scurvy controls we found lesions of the type of the scurvy plus infection, which in most instances were not so severe, but in some just as widespread and severe as in the experimental group.

We have not been convinced that the lesions are either identical or even closely similar to those of rheumatic fever.

DR. J. A. KEY, ST. LOUIS, MO.—About fifteen years ago Dr. Howe produced arthritic changes in the joints of animals by diet. Dr. Wolbach found the changes represented atypical scurvy. I have studied guinea pigs on a mild scorbutic diet. Some of them developed changes in joints; first a shedding of the synovial lining cells. I wonder about Dr. Rinehart's controls and whether a similar series of animals kept on the same diet would develop the joint changes without injections of streptococci. In my own experience when streptococci are injected into animals they either develop a purulent arthritis or the joints are unaffected. I have not produced therewith a condition resembling chronic atrophic arthritis, and I do not believe that any guinea pig, rabbit, or other laboratory animal ever develops rheumatic fever or atrophic arthritis. So where are we going to get animal streptococci to produce these diseases in animals?

DR. WALTER BAUER, BOSTON, MASS.—If a lack of vitamin C plays a rôle in the causation of rheumatic fever, why is the incidence of rheumatic fever no higher in infants suffering from scurvy?

I am very doubtful that vitamin C deficiency plays any important rôle in the production of atrophic arthritis for the following reasons: For the past five years each patient discharged from our hospital with the diagnosis of atrophic arthritis has been instructed to adhere to a high vitamin diet so far as his pocketbook will allow. The dietary calls for one eight-ounce glass of orange juice each day and one eight-ounce glass of tomato juice each day. Many of these patients have adhered to this diet for from three to five years, yet the results in this group are no different than in the group who did not adhere to the diet. If what Dr. Rinehart says is true, one would expect to see a difference in the therapeutic results in these two groups.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—Investigators studying artificial inoculation of laboratory animals with streptococci should understand the advantages to be derived from a knowledge of the serologic groups to which the particular strains they are using belong. Members of groups which are spontaneously pathogenic for man are generally not spontaneously pathogenic for animals, and groups pathogenic for animals have little disease inducing capacity for man. A common source of error is that we use so-called "human strains" to inoculate laboratory animals and expect these animals to have the same reactions as man. This was doubtless done in the experiments mentioned by Dr. Key;

but in Dr. Rinehart's work a group C strain was employed, a strain that is normally pathogenic for guinea pigs, and one that satisfactorily induces chronic lesions in these animals. This is a good example of using the proper experimental agents in conducting experimental studies.

DR. ERNEST E. IRONS, CHICAGO, ILL.—Some years ago we were studying chronic arthritis in hogs from which two organisms were isolated, a streptococcus and a short bacillus described in veterinary medicine. We inoculated a litter of little pigs with these organisms and had no trouble in producing chronic arthritis with persistent large articular deformities. In other laboratory animals no arthritis resulted from inoculations. As Dr. Swift stated, to get characteristic lesions in animals the organism used must be suited to the animal inoculated. To me this has always seemed to be one of the weak spots in animal experiments in respect to human disease.

DR. RINEHART (closing).—The studies of Dr. Wolbach referred to by Dr. Key have shown that vitamin C is essential for the normal metabolism of connective tissue and the formation of normal intercellular substances. His experiments were designed to demonstrate this fact, and dealt essentially with acute deficiency and the early reparative process following administration of the vitamin. His experiments therefore differ materially from those which I have reported. We have controlled all of our work, in studying the effect of deficiency alone, the deficiency combined with infection, and the infection in the presence of adequate nutrition. The guinea pig subjected to subacute or chronic vitamin C deficiency alone develops a chronic arthritis with many similarities to atrophic arthritis. It is probable that Dr. Howe's animals presented comparable changes. In this sense, the pathologic picture is truly that of scurvy but differs radically from the usual concept of the disease. The rôle of infection is of interest. If a factor of infection is added to the deficiency, the arthritis may be accelerated in development, and aggravated in intensity. This is not uniformly so, depending apparently on the type and virulence of the organism used. On the other hand, the various infecting agents alone in the presence of an adequate vitamin C, did not produce arthritis or other rheumatic manifestations.

I am glad that Dr. Swift and Dr. Irons emphasized the importance of using organisms from animal sources in animal experimentation. In our studies we used almost exclusively organisms derived from spontaneous guinea pig infections. I think this is one reason why Dr. Mote's studies have not been in accord with our own. Some of his experiments were made with organisms from other sources. In our own work a factor of infection in addition to the vitamin C deficiency appears essential for the production of the experimental picture resembling rheumatic fever. Even in using organisms that are naturally pathogenic for the species, we have found that they vary considerably in effectiveness.

Dr. Swift notes that our experimental findings have been essentially confirmed in his laboratory. On the basis of studies of storage and excretion of vitamin C and on clinical therapeutic studies, he concludes that "we have no real evidence that vitamin C is an important determining factor in the etiology of rheumatic fever." It must be noted that our knowledge of the metabolism of vitamin C is incomplete particularly when complicated by a factor of infection. Under such circumstances excretion of vitamin C in the urine may not denote saturation. It may be an expression of depletion or an inability to utilize the vitamin. Does the rheumatic process, once initiated, impair the absorption or utilization of vitamin C? In pernicious anemia certain infections impair the utilization of liver extract, necessitating great increases for an effective dose. Even though we could be assured that excretion of vitamin C implied saturation of tissues, this would give us no index of a past episode of deficiency as a basic contributory factor. With respect to a lack of immediately measurable improvement following the administration of large amounts of vitamin C, in cases of rheumatic fever, it would seem unlikely that saturation of the body with the vitamin would quickly restore a tissue change that has been acquired over a period of years or has resulted from repeated insult. A widespread and frequently severe connective tissue and vascular injury is found in rheumatic fever. The exact mechanism of this injury is unknown. Even though vitamin C deficiency may be a factor in the initial mechanism, another influence, probably infection, also operates. If this injury can be

repaired by vitamin C, time would appear essential. I wish strongly to emphasize the importance of this in the evaluation of clinical protective or therapeutic studies. In severe cases it would appear that much of the finer vascular bed and its connective tissue support would need to be reconstructed and this repair could probably start effectively only after cessation of the injury.

Dr. Shapiro has questioned the value or meaning of capillary resistance tests. We are aware of the limitations of this test as an index of latent scurvy. However, repeated observations over long periods of time indicate its significance. The capillary strength in general is reduced in rheumatic fever. Although the levels of capillary strength rose on administration of generous amounts of vitamin C, in many cases this return toward normal levels required several months, indicating a delayed restitution of tissue injury.

Dr. Bauer notes that his patients with arthritis have, on discharge, been instructed to take generous amounts of vitamin C and does not feel that improvement in this group is significantly different than other groups. Most diets recommended in arthritis contain liberal sources of vitamin C. We only suggest that subacute or chronic vitamin C deficiency may be *one* mechanism or a contributory factor in the development of atrophic arthritis. In some cases we may have to look for abnormalities in assimilation or utilization of vitamin C. The profound circulatory and other anatomic changes which characterize the disease in its subacute or chronic stage, even though vitamin C lack had contributed to their development, would be slow to respond to the administration of the vitamin. A prolonged clinical study of this phase of the problem is needed. Dr. Bauer also asks why the incidence of rheumatic fever is not high in scurvy. I do not know of any analysis of scorbutic cases from this standpoint. Clearly recognizable scurvy in this country is almost limited to infancy. It is not improbable that a childhood deficiency, perhaps more chronic and less intense, but just as real, would not be recognized by our usual standards.

In conclusion, I wish to reaffirm the broad experimental basis for the concept presented and to stress the necessity for a prolonged clinical study as the basis for final judgment.

INFLUENCE OF THE TONSILS ON RHEUMATIC INFECTION IN CHILDREN*

ALBERT D. KAISER, M.D., ROCHESTER, N. Y.

RHEUMATIC disease with its various manifestations has been clinically associated with tonsil infections for a considerable period of time. Extensive literature on this subject has appeared, which has not been in entire agreement. Tonsillectomy in selected children seemed to be followed by the subsidence of rheumatic manifestations and consequently this method of treatment was heralded as most successful. Such treatment was generally instituted until its practice became almost universal. However the good results seen in selected children were not always apparent when tonsillectomy was more commonly performed, so that the pendulum has gradually swung to the other extreme questioning whether tonsillectomy ever has any value in the treatment or in the prevention of rheumatic disease.

A review of the literature on the influence of tonsillectomy in rheumatic infection leaves one in doubt as to the exact relationship of the tonsils to rheumatic disease. There seems to be agreement on the observation that infection in the tonsils frequently precedes one of the rheumatic manifestations. On the other hand, many children subject to attacks of tonsillitis or sore throat do not develop evidences of rheumatic disease.

Assuming that infection in the tonsils occurs frequently in children who develop rheumatic disease, three questions naturally arise. First, Can the incidence of rheumatic infection in children be reduced if the tonsils are removed before rheumatic infection sets in? Second, Does tonsillectomy influence the course of rheumatic infection when the disease is once established? In other words, are there fewer recurrences of the disease? Third, Does the presence or the absence of the tonsils influence the outcome of this disease, or, stated otherwise, is the death rate increased or diminished by the treatment of the tonsils? If a satisfactory answer could be found for these three queries, it would be possible to state something definite about the influence that the tonsils exert on this disease.

In order to answer the first question on the incidence of rheumatic infection in children whose tonsils have been removed and in those whose tonsils have not been removed one must have information on a large group of children over a considerable period of time. A number of years ago a survey was undertaken in Rochester to obtain information on the general incidence of rheumatic manifestations in all of the school children. This information was obtained from the parents of the children. The parents of 48,000 children were inter-

*Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

viewed. Of this number, 20,000 children had been tonsillectomized and 28,000 had not had their tonsils removed. The information obtained in this survey stated the number of children who at some time during their life had clinical evidence of rheumatic infection. It was impossible, however, to determine whether the first rheumatic manifestation preceded the tonsillectomy, if done, or whether it occurred after the tonsils were removed. It did nevertheless give a general idea of the incidence of the various rheumatic manifestations in children.

Based on these data as obtained from the parents nearly all of the rheumatic manifestations occurred less commonly among tonsillectomized children. Rheumatic fever which is usually a severe type of rheumatic infection was reported with considerably less frequency in the tonsillectomized children. Among the children with their tonsils out there were 37 per cent fewer cases of rheumatic fever. Muscular rheumatism, termed growing pains, was reported only slightly

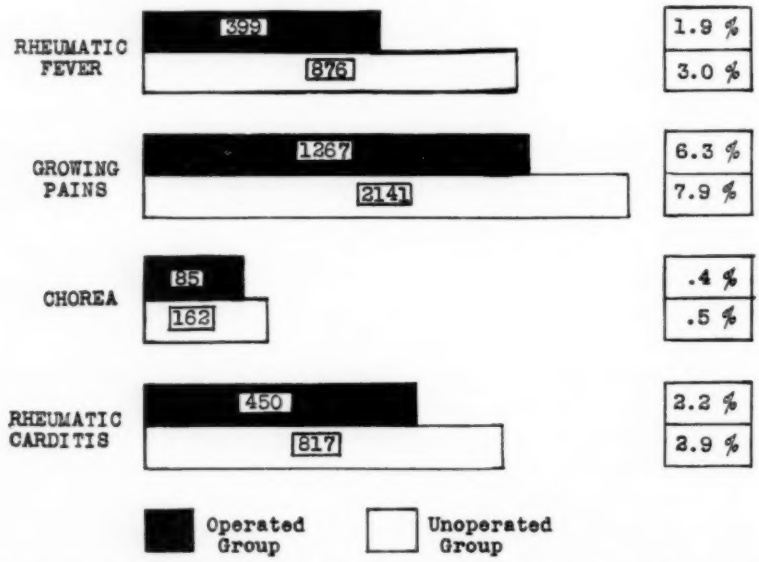

Fig. 1.—Chart showing comparative incidence of rheumatic manifestations in children on whom tonsillectomy has and has not been performed (based on the history of 48,000 school children of whom 20,000 had undergone tonsillectomy and 28,000 had not).

less often in tonsillectomized children. Chorea was noted with equal frequency in the two groups while rheumatic carditis was somewhat less common among the children with their tonsils out. In this survey many children among the tonsillectomized group reported some rheumatic manifestation. In some of them the rheumatic infection began before the tonsils were removed. If it had been known whether the tonsillectomy preceded the rheumatic infection or followed it, a more favorable comparison for the operated group might be noted. This statistical information based on the parents' history of the child leaves some uncertainty in the value of the data. It does, however, clearly indicate that rheumatic disease occurs in children whose tonsils have been removed, and it also seems highly probable, as noted in Fig. 1, that initial attacks of rheumatic infection are somewhat less likely to develop in children whose tonsils have been removed.

More accurate information dealing with the initial infection and the presence or absence of tonsils was obtained from an analysis of 439 children with acute rheumatic infection who were observed over a five-year period from January, 1925, to January, 1930. Familiar with the number of children whose tonsils have been removed at various ages, it was possible to compute the expected incidence of rheumatic disease among tonsillectomized children in the community.

TABLE I

COMPARISON OF THE ACTUAL WITH THE EXPECTED RATE IN TONSILLECTOMIZED CHILDREN AMONG 439 CASES OF ACUTE RHEUMATISM

AGE OF CHILDREN	TOTAL NO. CASES	EXPECTED NUMBER OF RHEUMATISM CASES WITH TONSILS REMOVED	ACTUAL NUMBER OF RHEUMATISM CASES WITH TONSILS REMOVED	NUMBER OF RHEUMATISM CASES THAT DEVELOPED BEFORE TONSILLECTOMY	PER CENT OF ROCHESTER CHILDREN WITH TONSILS OUT
Under 5 years	38	3.8	2	36	10
5-10 yr.	126	42.0	22	104	33
10-15 yr.	239	119.5	88	151	50
16-17 yr.	36	19.8	11	25	55
Total	439	185—42%	123—28%	316	

For all ages, as noted in Table I, the actual number of children who developed rheumatism after the tonsils were removed, was considerably less than the expected rate. The difference between the percentage of those actually operated upon and the expected percentage operated upon is 14 per cent. Utilizing an accepted formula for determining the standard error of difference, it develops that the difference, 14 per cent, is statistically significant. About one-third more children figured on a percentage basis developed their first attack of rheumatism when the tonsils were in than those who had been tonsillectomized. The full value of removing the tonsils in the control of rheumatic disease in children cannot be ascertained from the study of rheumatic children only, as has been done by various authors. If tonsillectomized children from the same homes, schools and cities over the same period of time and of similar ages show fewer cases of rheumatism than a like group untreated, there is justification in believing that early enucleation of the tonsils has protected some children against this infection. Such has been the case in large groups of controlled children in Rochester.

Additional information was obtained on the significance of the tonsils in the prevention of the various rheumatic manifestations from a study of 4,400 children. Composed of two equal groups, tonsillectomized and nontonsillectomized, the various rheumatic manifestations could be compared inasmuch as these children were observed for a period of ten years.

As noted in Fig. 2 chorea was known to have existed in 7 of the 2,200 children who were subsequently tonsillectomized. An equal number of children with chorea were found in the group of 2,200 children who were not later tonsillectomized. During the ten-year period following tonsil removal, 26 children developed chorea, while among the 2,200 children not tonsillectomized, 13 developed chorea. The seriousness of chorea can be judged by the occurrence of carditis associated with chorea. The incidence of carditis in the children who developed chorea

while the tonsils were in was 62 per cent. Among the children who developed chorea after the tonsils were removed, the incidence of carditis was 47 per cent. The inference is that chorea is not influenced favorably with removal of the tonsils, except in safeguarding slightly against the serious complication of rheumatic carditis.

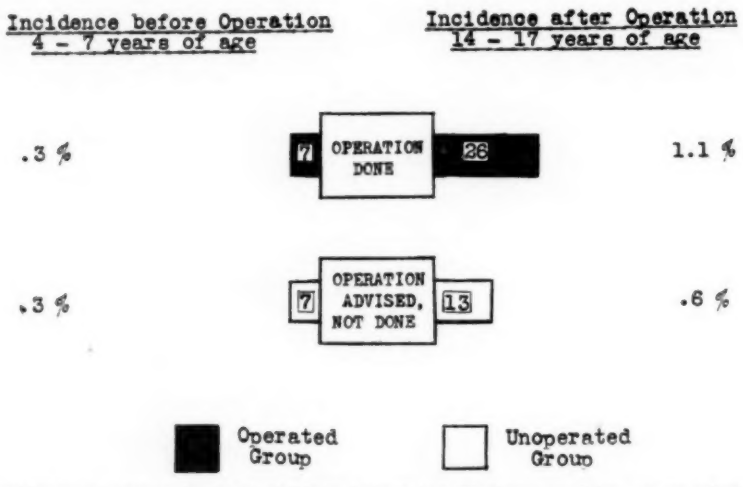

Fig. 2.—Incidence of chorea in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

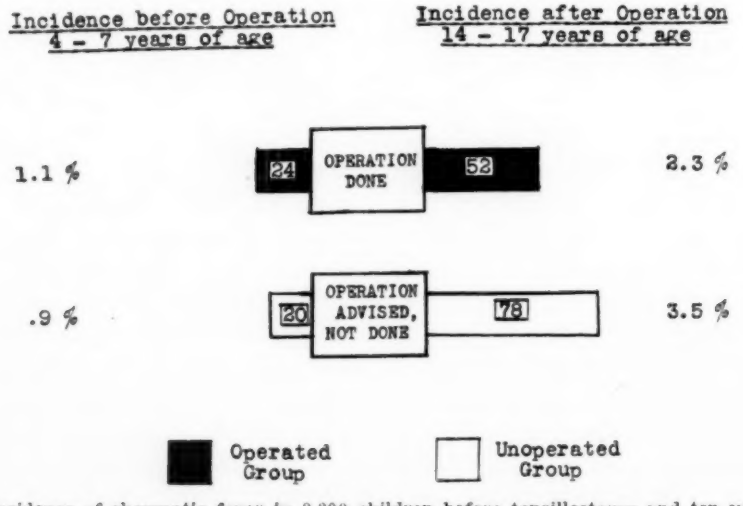

Fig. 3.—Incidence of rheumatic fever in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

The incidence of rheumatic fever was studied in the same two groups as shown in Fig. 3. Before removal of the tonsils 24 or 1.1 per cent of the 2,200 children had been afflicted with rheumatic fever, while among the control children, 20 or 0.9 per cent were similarly affected. During the ten-year period following tonsillectomy, 52 children or 2.3 per cent developed rheumatic fever, while 78 or 3.5 per cent of the control children were likewise infected. Realizing

that rheumatic fever occurs more commonly between five and ten years of age than before the fifth year, there is reason to believe that in this series, enucleation of the tonsils was responsible for about one-third fewer cases of rheumatic fever than in a similar group whose tonsils and adenoids were not removed. As with chorea, the occurrence of rheumatic carditis was studied. In the children who developed rheumatic fever for the first time after tonsil removal, 69 per cent developed rheumatic carditis. From this study it seems reasonable to conclude that removal of the tonsils offers some hope of escape from rheumatic fever. It occurred from 25 to 35 per cent less often in tonsillectomized children. The serious complication of rheumatic carditis is as likely to develop in children with rheumatic fever whose tonsils are out as in those whose tonsils are still present.

Though there is some doubt as to the relationship of so-called growing pains

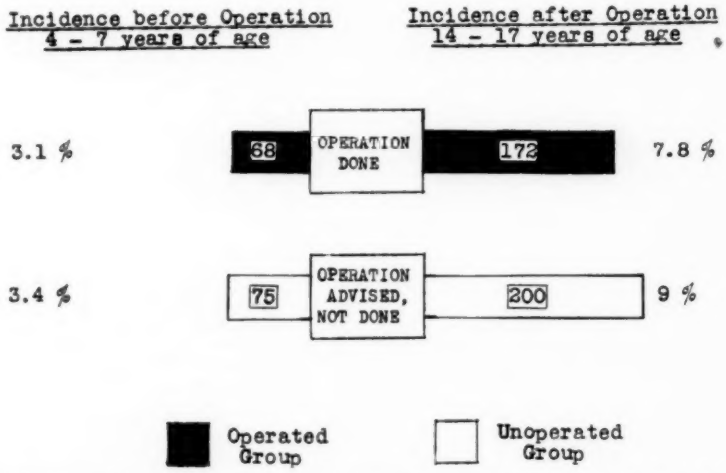

Fig. 4.—Incidence of growing pains or muscular pains in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

or muscular pains to rheumatism, it is now generally conceded that growing pains are mild manifestations of rheumatic infection. The incidence of this complaint with reference to the tonsils has been studied in the 4,400 children. Muscular pains as shown in Fig. 4, interpreted as rheumatic pains, occurred with equal frequency in the operated and unoperated group before the sixth year of age. During the school age period, 172 tonsillectomized children, or 7.8 per cent, were subject to this complaint, while 200, or 9 per cent, of the nontonsillectomized children were having growing pains. The less serious nature of this complaint is recognized in the infrequent complication of carditis. Evidence of carditis was detected in 16 per cent of the children subject to muscular pains in whom the tonsils had not been removed and in 18 per cent of the children whose growing pains manifested themselves for the first time after the tonsils were removed. The milder manifestations of rheumatism known as growing pains or muscular pains seem to be less influenced by the absence of tonsils than is rheumatic fever. It occurs somewhat less frequently in tonsillectomized children, but carditis is as likely to follow this mild rheumatic infection after the tonsils are removed.

Rheumatic carditis was studied in the 4,400 children similarly to the other rheumatic manifestations. During the ten-year period in which these children were observed, it developed that 1.1 per cent of the children contracted rheumatic carditis following tonsillectomy, while among the children whose tonsils were not removed, 1.3 per cent contracted rheumatic carditis. The difference is not significant. If one judges the value of tonsil enucleation to children who have had an attack of rheumatic fever, there is little to commend the operation for the control of rheumatic carditis. If, however, one analyzes a large child population where the incidence of rheumatic fever and chorea is known, it is evident that slightly less carditis exists in tonsillectomized children. This lessened incidence is due to fewer cases of rheumatic fever among tonsillectomized children, and a somewhat diminished incidence of carditis following chorea in tonsillectomized children. These three separate studies justify the statement that the tonsils have

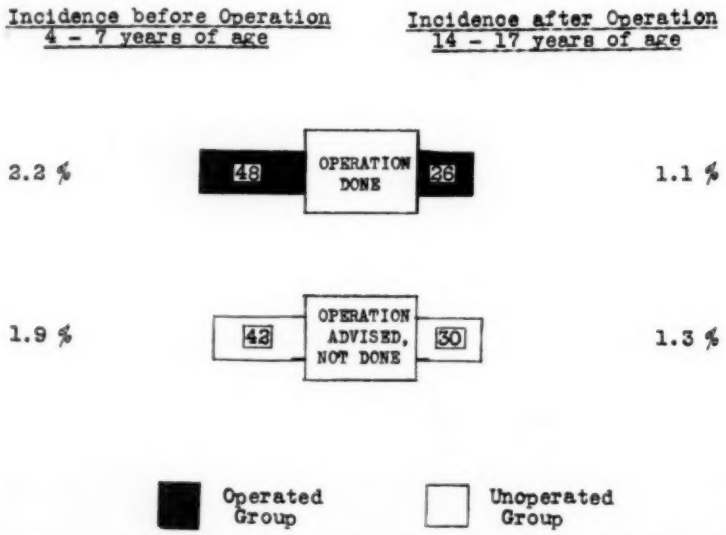

Fig. 5.—Incidence of rheumatic carditis in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

some influence on the incidence of rheumatic disease as recognized in children. They agree that rheumatic fever occurs about 30 per cent less often in children whose tonsils have been removed; that chorea occurs as often in tonsillectomized children as in those not so treated; that muscular rheumatism occurs slightly less often in the tonsillectomized children; that rheumatic carditis is found less often in the children whose tonsils have been removed.

In answer to the second query, Can recurrent attacks be influenced by tonsillectomy?—adequate data are available from several sources. Wilson, Lingg and Croxford prepared an excellent study of 413 rheumatic children in 1928 to determine the influence of the tonsils on recurrent attacks. In their survey, a careful correlation was made between the age of tonsillectomy and the age at which recurrent attacks occurred. It was brought out that recurrences occur in young children under nine years of age whether tonsils are removed or not while after ten years of age, recurrences are less common in both groups. Because of

their results they conclude that the routine removal of tonsils for the prevention of rheumatic heart disease in children is not justified by conclusive data. Poynton, on the other hand, believes that enucleation of the tonsils tends to stop severe recurrent throat infections, which on each occasion lay the rheumatic patient open to a recrudescence of the disease. In a study made by the author on 439 children who had acute rheumatism, the benefits of tonsillectomy in the prevention of recurrent attacks were not apparent.

TABLE II

INCIDENCE OF RECURRENT ATTACKS OF ACUTE RHEUMATISM WITH REFERENCE TO REMOVAL OF THE TONSILS IN 439 CHILDREN

AGE OF CHILDREN AT FIRST ATTACK	NUMBER IN WHOM FIRST ATTACK DEVELOPED BEFORE TONSILLECTOMY	NUMBER WHO HAD RECURRENT ATTACKS	NUMBER IN WHOM FIRST ATTACK DEVELOPED AFTER TONSILLECTOMY	NUMBER WHO HAD RECURRENT ATTACKS
Under 5 yr.	36	11—31%	2	1—50%
From 5 to 10 yr.	104	42—41%	22	10—45%
From 10 to 15 yr.	151	30—33%	88	19—21%
16 and 17 yr.	25	8—32%	11	4—36%

Recurrent attacks of rheumatism occurred as frequently in tonsillectomized children as in the untreated ones at all ages, except between the ages of ten and fifteen, when recurrent attacks are less common in both groups. The figures noted in Table II do not describe the seriousness of recurrent attacks, but in a general way, agree with the results obtained in Wilson's study. Though the number of recurrences of such manifestations as rheumatic fever, chorea, and muscular pains was not lessened by removal of the tonsils, it was demonstrated that carditis associated with recurrent attacks of rheumatic fever and chorea was somewhat less severe in the tonsillectomized children.

A solution was sought for the third question, Does the presence of tonsils in the rheumatic child influence the outcome of the infection? In a recent study made in Rochester the outcome in 597 rheumatic children was observed. In almost comparable groups the mortality rate was 13 per cent among the children whose tonsils were in during their rheumatic infection and 7 per cent among those whose tonsils were out at the time of the initial attack. This result suggests that the most serious type of rheumatic infection is more likely to occur in children whose tonsils are still present.

Though the removal of the tonsils fails to decrease the number of recurrences of rheumatic infections, there is a decidedly lower mortality rate among those

TABLE III

THE EFFECT OF THE TONSILS ON THE OUTCOME OF RHEUMATIC INFECTION IN 597 CHILDREN

TONSILS	NUMBER	DIED	ONE OR MORE RECURRENCES	NO RECURRENCES
Remained in	156	13%	46%	41%
Out at initial attack	187	7%	48%	45%
Out after initial attack	254	4%	44%	52%

children whose tonsils have been removed. If other studies show similar results, there is a definite indication in every rheumatic child for the removal of the tonsils.

There is statistical evidence based on controlled studies to justify the statement that tonsillectomized children are somewhat less likely to develop rheumatic manifestations. The lessened incidence of rheumatic infection is noted in cases of rheumatic fever and rheumatic carditis. Muscular rheumatism and chorea are as likely to occur in children whose tonsils have been removed as in those whose tonsils are still present.

The incidence of recurrent attacks of rheumatic manifestations is not influenced by tonsillectomy. If rheumatic disease occurs in children whose tonsils have been removed prior to the initial attack the number of recurrences is likely to be as great as in children whose initial rheumatic infection developed while the tonsils were still in. Where tonsillectomy was performed after the initial rheumatic infection the number of recurrences were no less than in the rheumatic children whose tonsils were not removed.

The end-result in rheumatic disease in children did show the influence of the tonsils. The mortality in nearly 600 rheumatic children was nearly twice as high in the children whose tonsils were in at the time of the initial attack. The absence of the tonsils apparently safeguarded some of the rheumatic children against the serious cardiac complications that are usually responsible for death.

Statistical and clinical data justify the removal of the tonsils in practically every rheumatic child until other factors that influence this disease are better understood.

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DISCUSSION

DR. RUSSELL L. CECIL, NEW YORK, N. Y.—Assuming that Dr. Kaiser's statistics are correct, that a tonsillectomized child has a 35 per cent better chance against having rheumatic fever, the question arises: When, in this climate, should tonsillectomy be done? I know of no more vexing problem to mothers in New York City whose children have repeated respiratory infections without joint manifestations, but with some fever and possibly some complications in the ears. An argument generally occurs between the pediatrician, the internist, and the laryngologist. The laryngologist is disposed to advise tonsillectomy in children earlier than the pediatrician or internist. I saw a three-year-old girl just a few days ago who had repeated respiratory infections, a little fever with each attack, tonsils that look infected, and involvement of the cervical glands. The question came up whether the tonsils should be removed at once, before any serious damage was done, or whether we should wait until she was five years old. In some respects it seemed best to wait, but I think a child who is having trouble with tonsils should have them removed before serious damage to other organs is done. In children with no more than the average number of respiratory infections, it is well to postpone tonsillectomy until they are five or six. I would like to hear from Dr. Kaiser on this important point.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—If Dr. Kaiser has concluded that tonsillectomy should be done in 100 per cent of children who have had rheumatic fever, I wish to take issue with him. All of us have seen serious even fatal flare-ups in quiescent juvenile

rheumatic disease immediately after a tonsillectomy. A definite diagnosis of rheumatic infection in children is often difficult to establish. If all children who complain of leg pains are subjected to tonsillectomy, we will only add a good number of useless tonsillectomies to the already large number of these operations being done constantly on insufficient ground. As a result of careful study of several hundred rheumatic children for a period of twelve years, I have concluded that tonsillectomy should be done no more often in them than in any other group.

DR. KAISER (closing).—In answer to the question as to whether 100 per cent of rheumatic children should have their tonsils removed, I should say yes. That is a rather small number after all, when one realizes that in any community almost 50 per cent of children are having their tonsils removed anyhow. Private school health records show that 85 per cent have had tonsillectomies performed. The reason that so many children have tonsillectomies is that the pediatrician and the otolaryngologist advised operation for frequent colds. If one recommends tonsillectomy in all individuals in the so-called rheumatic group, it will not run over 10 per cent. Tonsillectomy is most helpful to children with tonsillitis. It is in the rheumatic group that tonsillitis occurs. If we concentrated on that group we would have fewer disappointing results.

The most definite indication for tonsillectomy in children is a history of repeated attacks of tonsillitis. That is the one infection which most students of this problem believe leads to rheumatic fever. If we restrict our tonsillectomies to children who have tonsillitis, we will not have so many failures.

DISCUSSION ON PAPER BY DR. HUGH McCULLOCH, "INSTITUTIONAL PROVISIONS FOR THE CARE OF THE RHEUMATIC CHILD"*

W. D. Stroud, Philadelphia, Pa.

AT THE Children's Heart Hospital in Philadelphia, we have taken care of about 600 children with rheumatic heart disease in the past fourteen years. Three cardiologists and three pediatricians have been associated in caring for these children. We have concluded that tonsillectomized rheumatic children have done better than those seen in other clinics who have not had their tonsils removed. One of our requirements for admission to the Children's Heart Hospital is that no child will be admitted who has not had his tonsils removed. In addition to tonsillitis being an indication for removal of tonsils in the rheumatic child or in any child, we feel that a tonsillectomy should be performed earlier in children belonging to rheumatic families. Such children should be considered eligible for tonsillectomy at about the age of three years. To the parents of all these 600 children we have urged tonsillectomy for the other children in the family.

We feel that institutional care is of real benefit to children with rheumatic heart disease. The two objections I have heard raised against such institutions are these: if we put into such an institution a child who is not really rheumatic, he is exposed to the etiologic factor of rheumatic fever, through close contact with the others suffering from the disease. In the past fourteen years, we have had two epidemics apparently produced by streptococcic sore throats in nurses. Of 50 children in the institution at the time, only 12 or 14 had exacerbations of their rheumatic heart disease.

It has been argued that children of rheumatic families may, through contact with the disease, gradually develop less sensitivity to its etiologic factor. Removal to an institution and away from the family environment, might interfere with this. Since in such institutions these children are surrounded by others apparently hypersensitive to the etiologic factor, I believe such a criticism is not valid.

Points in favor of such institutions are, first, the general physical improvement which these children develop. Our hospital is within the city limits, surrounded by Fairmount Park. In such an environment, the general physical status of the children has definitely improved. They receive prolonged rest and at the same time, since a teacher is in attendance, are able to keep up with their studies and return to their own class in school after leaving the hospital. Thus, they do not suffer the introspection and inferiority complex common in children with physical handicaps, who must be associated with children much younger than themselves. One of the main objects of the institution is the education of parents. On visiting days, the head nurse lectures to parents and distributes literature of the American Heart Association. The children and parents learn the principles of hygienic care. A visiting nurse and social service workers follow this type of education in the home.

Such institutions provide graduate and undergraduate medical education, and an opportunity for clinical investigation.

For three years we have been using intravenous vaccine. The children who have received the vaccine have done no better than the control group. During a mild epidemic of reactivations, apparently produced through exposure to a streptococcic sore throat, as many of the vaccinated children developed exacerbations, as those in the control or unvaccinated group. In an effort to reduce the hypersensitivity of children to the etiologic factor in rheumatic fever, Dr. Joseph Stokes at the Children's Hospital in Philadelphia has been using a serum from whole blood of persons past the age of thirty-five in nonrheumatic families. Some children seem to have done well following this procedure.

*Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

FEVER THERAPY IN CHOREA AND IN RHEUMATIC CARDITIS WITH AND WITHOUT CHOREA*

LUCY PORTER SUTTON, M.D., AND KATHARINE G. DODGE, M.D., NEW YORK, N. Y.

FEVER INDUCED BY TYPHOID-PARATYPHOID VACCINE

DURING the past five years fever therapy has been used on the Children's Medical Service at Bellevue Hospital as the treatment of chorea. We were led to investigate this form of therapy because of the striking disappearance of a severe attack of chorea in a boy who became intoxicated by luminal and developed a high fever. A review of the literature revealed that the forms of therapy reported to have had definite effect on the duration of chorea, i.e., milk injections, nirvanol intoxication, and relapsing fever, had one factor in common, the production of fever. It had also been frequently observed that intercurrent infections had a beneficial effect on chorea. It was therefore difficult to escape the conclusion that it was the fever itself rather than the instrument which produced the fever which was beneficial in chorea.

After trying intravenous injections of typhoid vaccine with varying results, we began using typhoid-paratyphoid vaccine, with which we found we could produce fever almost at will. The reason that this vaccine was chosen as the means of producing fever was that it was cheap, easily available, reasonably safe and required no elaborate set-up or special technic. A method of procedure was developed which was given in detail in a previous publication.[1] In brief, the patient receives New York City triple typhoid vaccine (containing 1,000 million *B. Typhosus,* and 750 million each of Para A and B per c.c.) intravenously, beginning with a dose of 0.05 or 0.1 c.c., subsequent daily dosage being determined by the reaction of the patient to the previous one. The aim is to obtain a temperature of 104° to 106°. If necessary, a second dose on the same day is given. Treatment is continued daily, with occasional days of rest, until all signs of chorea have disappeared. In the mild and moderate cases this is seldom difficult to determine but in some children, particularly in those with severe chorea, where there has been marked hypotonia, it may be hard to decide just when the incoordination is due simply to weakness rather than to chorea. In these cases the child receives massage and occupational therapy. If the weakness decreases with increased activity, we feel safe in saying the attack is over. If the incoordination becomes worse, treatment is resumed. Figs. 1 and 2 show the temperature charts in two types of cases. Type 1 was a mild chorea, easy to treat, needing only small doses of vaccine to obtain the desired temperatures and responding well to a short course of vaccine. Type 2 was a severe chorea, difficult to treat, requiring a long course of treatment, and large doses of vaccine. In between these two

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Read at the Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases, June 10, 1935, Atlantic City, N. J.

types lies the majority of the cases. The average number of treatments in the first 150 cases treated by this method was 6.24. In the mild cases the average was 5.14 treatments; in the moderate 6.47 and the severe cases 8.88. The minimum number of treatments was 3, the maximum 18.

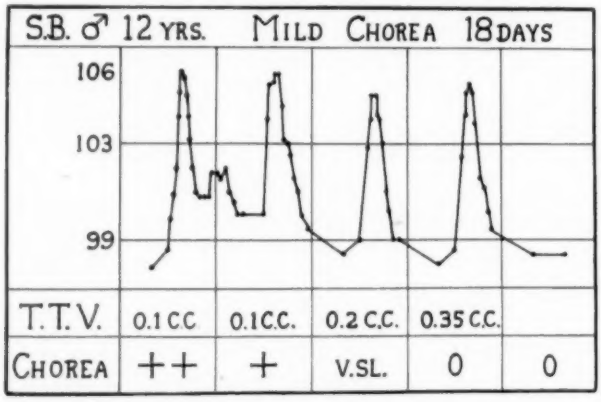

Fig. 1.

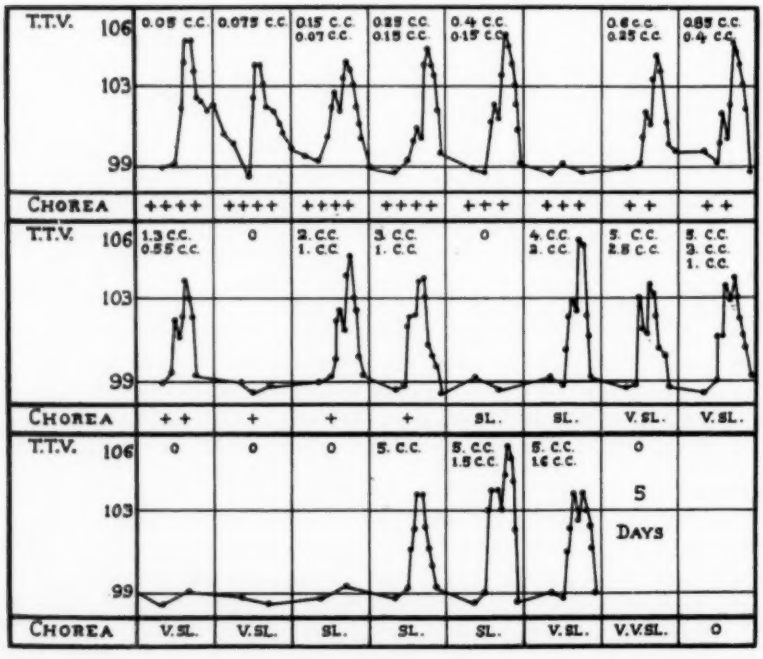

Fig. 2.

The results with fever therapy in the first 150 cases of chorea so treated have been previously reported.[1] For comparison we offered 150 cases treated on the same service before 1930 with various drugs, forms of physiotherapy and diet, plus rest in bed and isolation. Those who received fever therapy had definitely shorter attacks. The duration of chorea in the hospital in the group used for comparison, and the duration after beginning of fever treatment, are shown in Table I. This is also shown graphically in Fig. 3.

FEVER INDUCED BY RADIANT ENERGY

The disadvantages of producing fever by the intravenous injections of triple typhoid vaccine are the occurrence of protein shock, which may be very severe following the first two or three injections, and the inability to control the fever or to maintain it at the desired high level for any appreciable length of time. Investigation of other methods of producing fever led us to the conclusion that the use of radiant energy as developed by Dr. Stafford Warren and his co-workers[2] at the University of Rochester might prove superior to the intravenous vaccine method. We therefore had such an apparatus made, in which a patient's temperature may be raised to any desired level and maintained for as long a time as is necessary or the condition of the patient allows. Fig. 4 shows the type of temperature curve obtained by this means. Analysis of the first

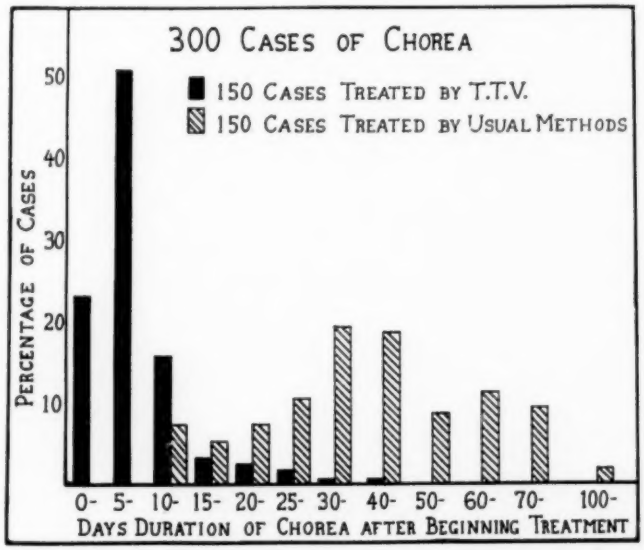

Fig. 3.

TABLE I

DURATION OF CHOREA

TYPE	NUMBER OF CASES	AVERAGE DURATION IN DAYS	RANGE IN DAYS
Mild:			
Comparative group	48	27.4	10- 67
Treated group	68	5.72	2- 14
Moderate:			
Comparative group	68	44.0	15-120
Treated group	57	8.56	3- 22
Severe:			
Comparative group	33	62.4	24-180
Treated group	25	15.8	5- 47
Whole Series:			
Comparative group	150	42.6	10-180
Treated group	150	8.5	2- 47

sixteen cases treated by this method shows that the results in terms of the duration of the chorea after one or two treatments are comparable to those obtained with a course of foreign protein induced fever (Fig. 5). Certain advantages of this method may be mentioned: (1) The fever is controllable. (2) One or two

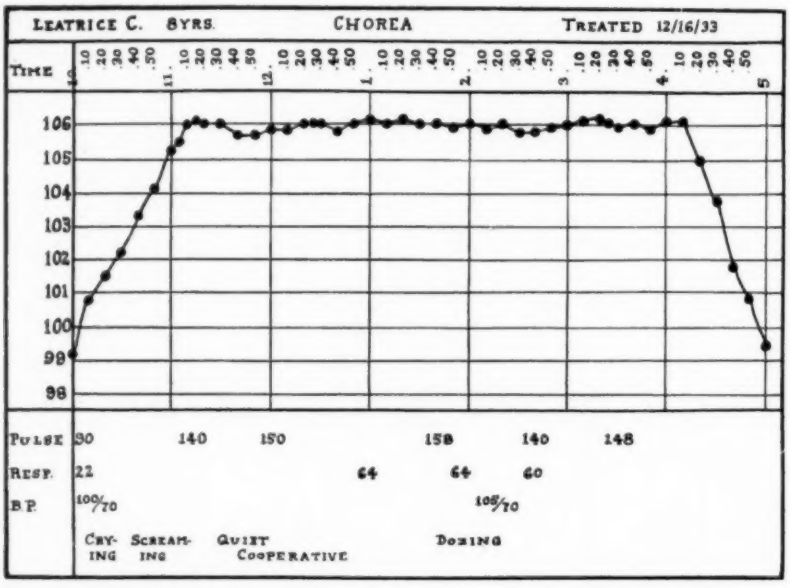

Fig. 4.

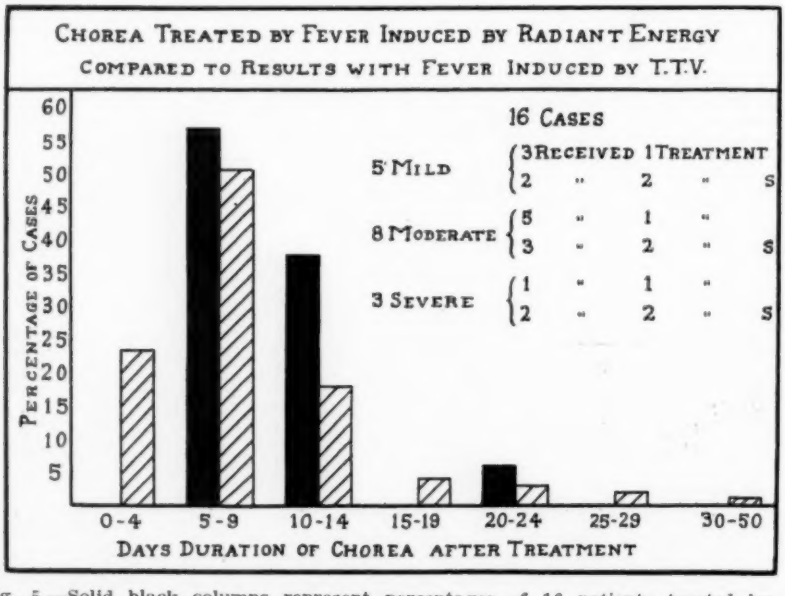

Fig. 5.—Solid black columns represent percentages of 16 patients treated by radiant energy. Cross-hatched columns represent percentages of 150 patients treated by intravenous triple typhoid vaccine.

treatments take the place of daily injections for a week or more of a foreign protein. (3) The patients appear distinctly less uncomfortable during treatment

with radiant energy than during treatment with foreign protein shock. (4) Except for the day of treatment the burden on the nursing staff is much diminished. The treatment of a larger number of patients may modify our results and lead us to change our opinion.

THE EFFECT OF FEVER THERAPY ON RHEUMATIC CARDITIS WITH AND WITHOUT CHOREA[3]

Among the first 200 patients who received typhoid-paratyphoid vaccine for chorea were 16 children with definite evidence of active rheumatic carditis at the time of treatment, and in addition 27 with clinically inactive heart disease. Among the latter group were 9 with mitral stenosis and insufficiency and 1 with both mitral insufficiency and stenosis and aortic insufficiency and stenosis. Our criteria for the diagnosis of active carditis were the presence of three or more of the following:

1. Fever
2. Tachycardia
3. Change in the quality of the heart sounds
4. Presystolic gallop sound at or just inside the apex
5. Development of new murmurs
6. Change in the quality of the murmurs present, especially the presence of a high pitched, shrill musical quality in the apical systolic murmur (sometimes described as "sea gull" quality)
7. Change in rhythm (heart-block or loss of sinus arrhythmia)
8. Electrocardiographic changes, chiefly prolongation of the P-R and QRS intervals
9. The presence of subcutaneous rheumatic nodules.

The effect of fever therapy on the clinical signs of active carditis in 5 illustrative cases is shown in Table II. In the whole group of 16, 9 had lost their clinical signs of activity by the time the chorea was over and the treatment stopped, and the remaining 7 were clinically inactive within seven to ten days after the end of the treatment. We appreciate the fact that there are cases in which the signs of active carditis subside after a short time at rest in bed, but on the other hand the tendency to chronicity of the rheumatic infection is well known.

While we did not think that the disappearance of the signs of active carditis in the majority of cases by the end of treatment was necessarily the direct result of fever therapy, we believed that it was sufficiently suggestive to justify an investigation of the effects of fever on various forms of rheumatic heart disease without chorea. Up to the present time we have treated with fever produced by radiant energy seven children with subacute rheumatic carditis without chorea, and one child with a very severe acute carditis accompanied by polyarthritis and chorea. These patients were given a fever of approximately 106° for from two to five hours at a time; five of them received two treatments each. All of these children showed decreasing signs of active infection immediately or within a comparatively short time after treatment. Figs. 6 and 7 show graphically the clinical course in the hospital of the first two patients treated by this means.

I. B. (Fig. 6) was seven and one-half years old when she was admitted in November, 1933. She had had polyarthritis at five and six years, and is said to have had heart disease since the age of three years. The present illness began

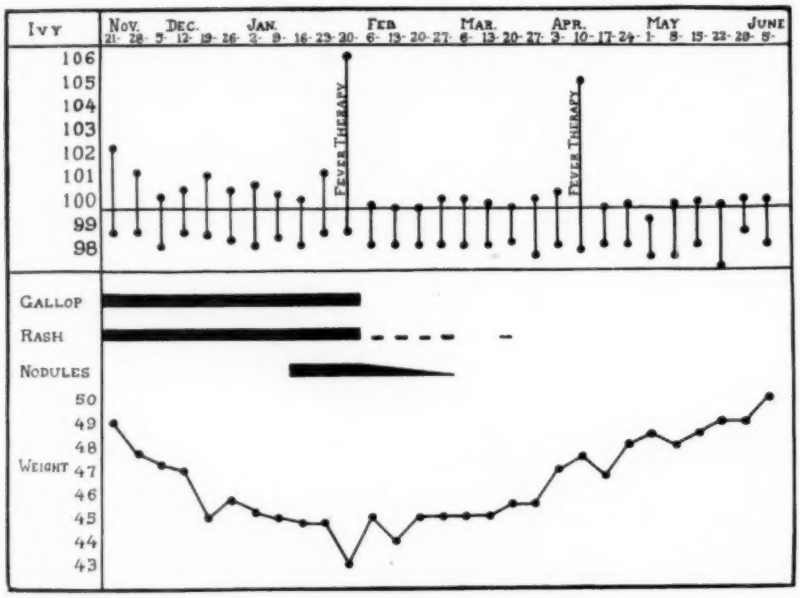

Fig. 6.

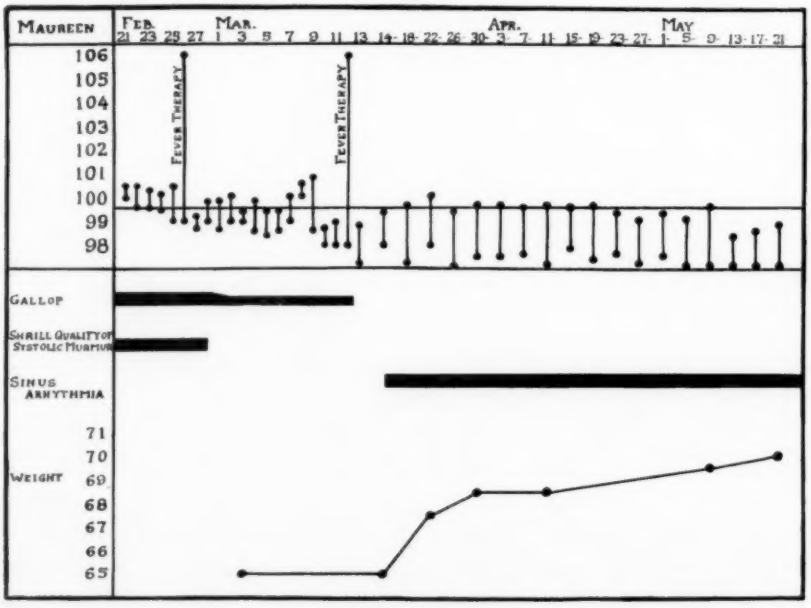

Fig. 7.

two weeks before admission with the development of an erythematous rash. Three days later she began to feel tired, to have migratory joint pains and afternoon fever. On admission she appeared acutely and chronically ill, her tempera-

ture was 101°, there was widespread erythema marginatum, her heart was enlarged, there was tachycardia, presystolic gallop, an accentuated P_2, a loud harsh systolic murmur at the apex transmitted to the axilla and base, and a low pitched diastolic murmur. The persistence of the signs of active infection during the first ten weeks of her stay in the hospital is shown in the chart. The striking subsidence of these signs following one fever treatment of four hours between 104° and 106° is also shown. What does not show was the change in the child's general appearance and attitude. Within one week after treatment she had changed from a listless lackadaisical child with a poor appetite, to a lively, active one, bright and interested in her surroundings, and with a ravenous appetite. She was given a second treatment in the ninth week after the first, because al-

TABLE II

NO. ADM. CARDIAC DIAGNOSIS	SIGNS OF ACTIVE CARDITIS	DURATION THERAPY	DURATION OF CLINICAL SIGNS OF CARDITIS	DISCHARGE DIAGNOSIS
1. a. Rheum.* b. Carditis c. S.T. d. E. & F.	Tachycardia, development of systolic and diastolic murmurs under observation	8 days	End of therapy; rate slower, murmurs softer 10 days later; rate 78, S.A. present	a. Rheum. b. M.I. & S. c. S.A. d. 11a.
2. a. Rheum. b. E.H., M.I. Carditis c. S.T. d. I.	Fever on admission, tachycardia, gallop. Quality of systolic, presence of diastolic	8 days	End of therapy; rate 80, no gallop, S.A. present. 4 days later; diastolic murmur no longer heard	a. Rheum. b. E.H., M.I. c. S.A. d. I.
9. a. Rheum. b. Carditis c. S.T. d. E. & F.	Tachycardia, gallop, development of systolic murmur	8 days	After 1 fever; no gallop, rate 100. End of therapy; rate 88, murmur less loud. 10 days later; no murmur	a. Rheum. b. -- c. S.A. d. F.
14. a. Rheum. b. Carditis c. S.T. d. E. & F.	Fever, tachycardia, gallop. Development of diastolic murmur, prolonged P-R interval	17 days	5 days after beginning of therapy; rate 80-90. No gallop. P-R interval normal before end of therapy	a. Rheum. b. -- c. S.A. d. E. & F.
16. a. Rheum. b. E.H., M.I. Carditis c. N.S.R. d. I.	Gallop, high pitched, shrill systolic. Presence of diastolic	8 days	5 days after beginning of therapy; no gallop, systolic soft and low pitched. No diastolic heard	a. Rheum. b. E.H., M.I. c. N.S.R. d. I.

*Diagnoses were made according to the criteria for the classification and diagnosis of heart disease of the Heart Committee of the New York Tuberculosis and Health Association. Abbreviations used are: E. H., enlarged heart; M. I., mitral insufficiency; M. S., mitral stenosis; N.S.R., normal sinus rhythm; S. A., sinus arrhythmia; S. T., sinus tachycardia; E., possible heart disease; F., potential heart disease; I., functionally able to carry on normal activity; 11a, functionally able to carry on with slightly limited activity.

though her general condition continued to be good, her temperature on two occasions was above 100, and her sleeping pulse rate began to be slightly elevated. Following this her progress was steadily uphill.

M. M. (Fig. 7) was twelve years old when admitted in February, 1934. She had had repeated attacks of chorea since the age of four and one-half years, but no other rheumatic history. She had been followed by us since September, 1931, when she was treated with fever therapy for a moderate chorea. Since that

time she had had two very mild attacks of chorea. Her heart had never been enlarged but there had been an apical systolic murmur, transmitted slightly, present from the time of her first admission, and a diastolic murmur had first been heard in December, 1932. For two months previous to admission the mother had noticed tachycardia; dyspnea on climbing one flight of stairs had developed and the child had been complaining of frequent precordial pain. Two weeks before admission she had had a sore throat and had been worse since that time. On admission her temperature was 100.4°, heart rate was 130-140, there was a marked presystolic gallop, an apical systolic murmur with a high pitched shrill musical quality and a short middiastolic; no sinus arrhythmia was present. In view of the observed tachycardia and precordial pain of two months' duration, she was treated promptly without long observation in the hospital. The first treatment was for four hours at 105° to 106°, and the second, two weeks after the first, was for three hours at 106°. Following the first treatment the signs of activity decreased but they did not completely disappear until after the second. The most striking immediate change was the disappearance of the shrill musical quality of the apical systolic murmur. There was also the same change in the general appearance and behavior that was shown in the first case.

CONCLUSIONS

Fever, by whatever means produced, is a satisfactory method of treatment of chorea, in that the duration of the attacks is thereby appreciably shortened.

The presence of subacute carditis or of inactive rheumatic heart disease is not a contraindication to the use of fever therapy in treating chorea.

The subsequent uphill course of patients with subacute rheumatic carditis who received fever therapy suggests that fever may be of benefit to such patients. We believe that further investigation is warranted.

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DISCUSSION

DR. PHILIP S. HENCH, ROCHESTER, MINN.—There is a frame of mind among certain physicians that all "machine-medicine" is tinged with quackery, that even if the deus ex machina is a benign god, he should nevertheless be considered an unorthodox deity. Such physicians look with a suspicion, not always unjustified, upon anybody who uses machines in therapy. Fever therapy has had its origin in the laboratories of scientists of national and international repute. Its clinical utilization has so far been entrusted almost exclusively to physicians associated with large clinics and research institutions, men familiar with accurate methods for such investigations. Nevertheless, fever therapy is still enjoying its "honeymoon period" and reports thereon are still apt to be a bit enthusiastic.

The report of Drs. Sutton and Dodge is expressed in conservative terms. Their results are in general agreement with those reported at the Fifth Fever Therapy Conference in Dayton last May. Of a total of twenty-five cases of Sydenham's chorea treated by Hefke, Bierman, Schnabel, Schmidt, and Metz, about twenty cases (80 per cent) were apparently notably benefited even though several had previously not been relieved by reactions to typhoid vaccine given intravenously. A number of patients had carditis or mitral endocarditis; this was not considered a contraindication to fever therapy. Usually four or five treatments of three hours each at 105° to 106° F. were given.

At the Mayo Clinic under the clinical observation of Drs. Helmholz and Amberg ten cases of Sydenham's chorea have been treated with fever therapy by Drs. Desjardins and Popp. The age of the patients averaged ten years (youngest seven, oldest fifteen years). The duration of infection ranged from one week to four years. From four to twelve (average six) fever sessions of three hours each were given. The patients have been observed for from six to fourteen months since treatment. One was remarkably relieved, eight were definitely benefited. One to whom inadequate fever was given was not helped. A temperature of 104° to 107° F., not lower, is advocated.

From these various preliminary experiences it seems proper to agree with Drs. Sutton and Dodge that fever therapy is a helpful and promising form of therapy for chorea.

DR. JOHN R. MOTE, BOSTON, MASS.—It seems from the results presented that patients with chorea are helped by the use of typhoid vaccine or by artificial fever. In considering such results, however, it is necessary to keep in mind that chorea is a symptom-complex and not a disease entity, the diagnosis of which is frequently difficult and not uncommonly open to question. More difficult still is the determination of cessation of the disease. This in our experience has been a repeated issue for discussion in following the clinical course of many patients. In any condition where there may be wide differences in the criteria of complete recovery the results of the use of any therapeutic agent must be open to considerable individual interpretation. Typhoid vaccine treatment has not been used on an extensive scale at the House of the Good Samaritan. In our limited experience with this therapeutic agent in this condition, we noted that in all instances the choreiform movements were definitely decreased, but unfortunately only temporarily so. In most instances they were not given quite such intensive treatment as that used by Drs. Sutton and Dodge. Since our results were neither complete nor permanent we have not felt that such severe treatment was indicated in the usual case of chorea. In the severe and exhaustive form of the disease typhoid vaccine may be an indicated form of therapy.

Dr. T. D. Jones and Dr. E. F. Bland have recently completed the analysis of a follow-up study of 1,000 consecutive chorea and rheumatic fever patients at the House of the Good Samaritan who have been followed over an average period of eight years since the onset of their disease. In this study chorea was taken as one manifestation of rheumatic fever and analyzed as such, and all other manifestations of rheumatic fever were considered other evidence of rheumatic fever. There were 482 patients who had chorea as one of the manifestations of rheumatic fever whereas 518 patients had other evidences of rheumatic fever without chorea. Of the 482 patients who exhibited chorea, 54 per cent had clinical evidence of heart damage; in contrast to this, of the 518 patients who had only other manifestations of rheumatic fever, heart damage was present in 86 per cent of the cases. When the group of 482 patients who had chorea as a manifestation of rheumatic fever is further subdivided into those who had chorea as the only manifestation of rheumatic fever, and those who had in addition to chorea other evidence of rheumatic fever, it was found that the incidence of clinically demonstrable heart disease in the former group of "pure" chorea was only 3 per cent. The latter group of patients having chorea with other evidence of rheumatic fever had an incidence of 73 per cent of heart disease, clinically detectable. Therefore, instead of being a grave manifestation of rheumatic fever, chorea in itself is seen to be a mild manifestation. And patients with chorea alone show no special predilection to heart disease unless other evidence of rheumatic fever occurs. On the other hand, any patient with chorea and with other evidence of rheumatic fever, either laboratory or clinical, should be treated as any other individual with active rheumatic fever.

A year ago Drs. Jones and Bland reported on the use of single intravenous doses of typhoid-paratyphoid vaccine in 12 rheumatic fever subjects and noted definite recurrences in six instances. If this is even an uncommon occurrence, it is a contraindication for the use of vaccine therapy where there may be evidence of rheumatic fever other than chorea.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—When should fever therapy be applied in a case of rheumatic fever? In former times "hyperpyrexia rheumatica" was one of the most dreaded and fatal complications of acute rheumatic fever. It is conceivable that if this type of therapy were applied to a patient at a time when the heat regulating mechanism was very

unstable, it might place him in a state of uncontrollable hyperpyrexia, when later it might not. So many rheumatic children have evidence of low grade fever and persisting infection, that any relatively safe measure which promises aid in eliminating these symptoms should receive a thorough trial. Our own experience with fever therapy has been too limited to permit of seasoned judgment.

DR. E. STERLING NICHOL, MIAMI, FLA.—In discussing fever therapy in patients with active carditis one should differentiate between fever therapy produced with foreign protein and that induced by heat. When I was an interne on the service of Dr. Joseph L. Miller in Chicago twelve years ago, we gave intravenous typhoid vaccine to all patients with rheumatic fever *without* carditis. At that time we felt that cases with active carditis did not tolerate foreign protein therapy well. Is your experience with foreign protein in active carditis similar to that with fever therapy induced by the "hot-box"? The latter may be safer than the use of foreign protein.

DR. JOHN WYCKOFF, NEW YORK, N. Y.—This paper makes three propositions: the treatment of Sydenham's chorea with foreign protein fever, and with artificial fever, and the treatment of rheumatic carditis with artificial fever.

In our section of the country we do not feel that chorea is such a simple manifestation of rheumatic fever as Dr. Mote seems to think. The course of chorea can be tremendously shortened and the symptoms almost immediately alleviated by the use of foreign protein. As a result of such treatment chorea patients have practically disappeared from the services of the Bellevue Hospital.

With artificial fever therapy the results are even better. The temperature can be controlled. If the patients get too excited or ill the temperature can immediately be reduced. In every way it seems to be a more effective method of treatment.

We are most interested in the effects of fever therapy on patients with definite, active rheumatic carditis. The number of such cases treated by Drs. Sutton and Dodge is very small, but in practically every one of their sixteen patients, a definite change in the course of the disease is reported. Enough time has not elapsed for one to say that such cases will show fewer relapses than those which have been allowed to run the natural course of the disease.

DR. SUTTON (closing).—Though chorea seems to be the least serious of the rheumatic manifestations, it does lead eventually to cardiac damage, one reason for believing that rather heroic treatment is justified. Chorea keeps children out of school for weeks and months and is not a pleasant disease to have. Some children return asking for more treatment. They would rather have the foreign protein reaction and then be able to go back to school than to lie in bed for weeks.

In using foreign proteins we aimed for a high fever and not just for a temperature of 102°. Although we have treated 300 or 400 cases of chorea with typhoid-paratyphoid vaccine we have never noted any bad effect and never induced an attack of carditis or polyarthritis.

For the treatment of carditis we selected cases of low grade rather than acute activity. We did not treat children who had histories of congestive heart failure. We treated one acutely ill child who had chorea and also a severe acute carditis which had followed an acute polyarthritis just before her admission to the hospital. Although she was not definitely or immediately benefited by the two fever treatments she stood them well, even though during the first hour of fever her pulse rate became very rapid. Two weeks later when we gave her a second treatment she had no dyspnea and could lie flat in bed. Her pulse did not become so rapid. Now she is much better; indeed she is the picture of health.

In using hot packs for the production of fever we had one fatal result. With typhoid-paratyphoid vaccine we have had no fatality. In our first report we included the case of one child whose temperature was raised by means of a blanket pack; her temperature got out of control and went up to 109°. Clinically she had shown no evidence of activity, but at autopsy there was a definite verrucous endocarditis of the mitral valve and an old endocarditis of the aortic valve. Though the temperature was brought down she died the next day.

A THEORY CONCERNING THE MECHANISM AND THE SIGNIFICANCE OF THE ALLERGIC RESPONSE

WARREN T. VAUGHAN, M.D., RICHMOND, VA.

IN THE three hundred years since Harvey introduced the experimental method this has become the most useful procedure in the study of normal and pathologic physiology. Given an abnormality such as albuminuria, one can study the anatomic changes in the organ responsible for the production of urine; establish functional and organic changes in the blood and tissues and their relationship with the abnormal renal findings; and produce organic changes in animals sufficiently like those observed in man to facilitate further study of the problem. It is true that the nephritic changes produced in animals are not identical to those observed in man, but the parallelism is clear enough to permit studies which have widened our knowledge of renal disease.

The same may be said of many other functional and organic pathologic states. Their reproduction or near-reproduction in animals has facilitated research and has broadened our understanding.

Curiously, in one group of maladies, the experimental method has anticipated itself, causing much confusion. The customary procedure has been to select a problem for study; to devise a program for the production of an analogous lesion in experimental animals; to accomplish this; and then to proceed with those studies which cannot be suitably carried out in man himself.

But in the late nineties the reverse situation manifested itself. Diphtheria antitoxin had been discovered by Von Behring, confirmed by Roux, and was being produced in volume by the pharmaceutical supply houses. Guinea pigs used for potency tests reacted in curious ways. Once having been used, they were likely to die suddenly and unaccountably if used a second time. Richet and Hericourt, later Portier and Richet, observed a similar curious phenomenon following repeated parenteral injections into dogs, of sea anemone extract. Richet described a new phenomenon, not comparable with anything previously recognized as disease in man. He established two fundamental points which remain unquestioned: (a) that a foreign organic substance, though harmless in a given dose on first injection, might be most harmful, even fatal, following a second injection in the same dosage; and (b) that an interval of several days must elapse between the first and second injections before the substance becomes poisonous.

Except for the few curious reactions in human beings following the injection of diphtheria antitoxin that were then making their appearance, there was no analogy in human disease.

It was not until 1906, four years after Richet had propounded his theory, that Wolff-Eisner suggested that hay fever might be an anaphylactic phenomenon. It was not until nine years after Richet's work that Noon and Freeman conclusively demonstrated the accuracy of this suggestion. There was a lapse of

eight years before Meltzer, basing his suggestion on Auer's observation of broncho-constriction, first suggested (1910) that asthma might be an anaphylactic disease. Not until 1921 did Duke demonstrate the anaphylactic basis of gastrointestinal allergy. Thirteen years elapsed before Rohrer suggested that migraine might be associated with this curious experimental phenomenon and a full twenty-five before Vaughan proved the association by allergic methods. Twenty years elapsed before Vaughan demonstrated a similar relationship in certain cases of mucous colitis.

We may say, however, that after 1910 investigators were beginning to realize that a group of clinical diseases might be explained on the basis of the knowledge that was accumulating concerning experimental anaphylaxis or protein sensitization. Gradually new diseases were being added to the list, diseases which had no apparent intimate association with one another. We commenced to speak of the allergic diseases.

The next phase was a rather acrimonious discussion concerning the mechanism of the phenomenon and a similar debate regarding the similarity or identity of clinical allergy as observed in human beings and experimental anaphylaxis as seen in animals. Both debates continue, but with decreasing momentum. With regard to the second, which holds our major present interest, there is still wide divergence of opinion. There are many who insist that points of dissimilarity between clinical allergy and anaphylaxis render an actual identity impossible. The principal points made are: (1) that anaphylaxis is an antigen-antibody phenomenon in which antibodies and precipitins can readily be demonstrated in the blood, while such substances are not present in the blood of allergic human beings; (2) that animals may be sensitized with ease while it is almost impossible to render human beings artificially hypersensitive; (3) that though protein sensitization can be transmitted passively from mother to offspring, active hereditary transmission cannot be accomplished in animals, while human allergy is predominantly an hereditary malady.[1]

These are points of difference which I have always felt were nonfundamental and that further research would eventually reconcile.

If the sequence had been reversed, if there had existed a certain clearly recognizable disease complex which we shall call allergy, and animal research had followed rather than preceded a recognition of the clinical entity, the studies of experimental anaphylaxis would have been accepted with little or no question, as observations elucidating the phenomena of allergy. There are points of difference between nephritis in human beings and experimental uranium nephritis, but, those differences being recognized, investigators do not quibble as to whether the experimental disease is analogous, within the limits of the study. But in allergy for some curious reason, since the experimental observations antedated the clinical application, more attention has been bestowed upon the discrepancies than upon the fundamental similarity.

It shall be my purpose in this communication to demonstrate the basic identity of the two; to present the various apparently unrelated allergic manifestations as an integrated symptom-complex; and to explain how these diverse symptoms actually represent a rational coordinated purposeful response. This

explanation is predicated upon the assumption that the allergic response, no matter what its clinical manifestation of the minute, is as much a disease entity as is hypertension, with its associated arteriosclerosis and cardiorenal pathology. The difficulty in the past has been that, since no single organ can be identified either functionally or structurally as the primary seat of the malady, it has been difficult to select a point of departure for study.

Our theory can be most clearly presented by a series of dogmatic statements, each of which is followed by clinical or experimental observations.

I. ALL PERSONS ARE POTENTIALLY ALLERGIC

1. *There is no fundamental difference between clinical allergy and experimental anaphylaxis.*—The three chief points of contention made by those who deny a basic identity have been mentioned. The absence of antibodies in the blood of human allergies, at least so far as our present methods can demonstrate, is granted. That there is some sort of antibody in the blood is demonstrated by the phenomenon of passive transfer by the Prausnitz-Küstner method. The designation "reagin" has been proposed[1] in recognition of their presence and to emphasize that they are probably different from the antibodies of laboratory animals. In other words there is something in the blood with which we can produce passive transfer in human beings. It cannot be identified by precipitin tests or by complement fixation reactions.

For a time it was believed that precipitin represented the antibody, but there is now some doubt regarding this, and many believe that while precipitins accompany antibodies, they are not the antibodies themselves.

Doerr and Russ found that the ability of serum to passively transfer anaphylaxis is porportionate to its precipitin content. However, as stated by Seegal,[2] it is sometimes possible to transfer hypersensitiveness with serum in which no precipitin can be demonstrated. "It may therefore be that the antibody responsible for the transfer of anaphylaxis is not a precipitin, but some substance which increases in amount in the serum of immunized animals coincidentally with the precipitin." Matsumoto[3] has observed that in guinea pigs precipitins may persist in organs and tissues long after they have completely disappeared from the blood. According to the prevailing hypothesis of anaphylaxis, the reaction is cellular rather than humoral, and the presence of tissue antibodies is therefore of much greater importance than that of antibodies in the blood serum. Until recently the demonstration of tissue antibodies has been difficult or impossible. Khorazo[3] however has recently prepared practically pure tissue juice by breaking up the individual cells under high pressure. Seegal and Seegal[2] have demonstrated cytoplasmic antibodies in such tissues. They found, further, that typhoid agglutinin existed in the tissues in from two to four times its concentration in the blood. Occasionally they even demonstrated agglutinins in the tissues when none at all were demonstrable in the blood. Therefore, whether antibodies and precipitins are identical or not, the fact that these are not present in human allergies in no way invalidates an identity between clinical allergy and experimental anaphylaxis.

The second point, that it is difficult or impossible to sensitize human beings, will be discussed in section 7.

With regard to the third point, the recent investigations of Ratner[4] have shown that it is possible to transmit active sensitization in animals from mother to offspring.

2. *The allergic response is not limited to protein but may be made to a large variety of nonprotein substances.* The reaction to protein is the most dramatic, was the first type observed and is the most easily studied, since it is so easily reproduced in animals.

The first nonprotein substances added were those drugs which sometimes caused symptoms indistinguishable from allergy when administered enterally or parenterally. The early suggestion of Wolff-Eisner, the investigations of Obermeyer and Pick and of Jadassohn, and the more recent conclusive work of Landsteiner on haptenes have provided a rationale for the interpretation of drug allergy, in terms of protein sensitization.

Typical allergic symptoms, due to heat, cold, light and effort, appear to bear no connection with protein sensitization. This is likewise true of contact allergy to nonnitrogenous substances, although at present we know nothing concerning the possibility of a union of these substances with the proteins of the superficial tissue cells.

The possibility, as developed principally by Avery, that certain carbohydrates may sensitize although they cannot shock unless conjugated with specific proteins should be mentioned.

The present theory does not require that protein be implicated as the basis of all allergic responses. At the same time such an eventuality would not invalidate the hypothesis.

3. *There is no fundamental difference between the allergic and the so-called nonallergic individual. The response of the allergic person differs from the nonallergic in degree, not in kind.* Rackemann[5] (1930) wrote, "It seems proper to assume that hypersensitiveness is acquired in most cases and probably in all. What we call allergy may well be nothing more than anaphylaxis in man. . . . The production of antibodies in general is a normal function. Allergy is a reaction of a particular kind which is characterized by the easy formation of cellular antibodies in great abundance. . . . When the individual has several different allergic symptoms at one time; when his family history shows allergy in his antecedents, in his children or perhaps in both; when his symptoms are severe or when his skin tests are large, that individual may be assumed to have an easy tendency to develop hypersensitiveness. He is allergic only in this sense."

Vaughan[6] (1933), in a study of a series of cases of major allergy and minor allergy, observed no fundamental difference between either of these groups or the so-called nonallergic group. He concluded, "Allergy is not a pathologic state. It is a pathologic exaggeration of a normal physiologic response."

Rackemann[7] (1933) found no fundamental difference in the immunologic response, the development of typhoid agglutinins and other agglutinins, in allergies and in nonallergics.

Rackemann and myself were, so far as I have been able to determine, the first to express the belief that there is no fundamental difference between the allergic individual and the nonallergic. All gradations between the two groups exist.

4. *Clinical allergy is much more common than has been hitherto suspected.* The surveys of Cooke and Vanderveer[8] and of Piness and Miller[9] would indicate that not over 10 per cent of the population is allergic.

I, however, found in a survey of an entire community[10] that while the frankly allergic did comprise about 10 per cent, there was an additional 50 per cent who had had some clear-cut allergic manifestation at some time in their past experience. I called these *minor allergics* in contrast to the first group, of *major allergics*. There was, in general, a distinct difference between the two groups, in that the minor allergies were able almost without exception to designate the cause of their symptoms while the major allergies could not do so. The minor allergic or fortunate allergic was sensitized to some substance with which he came into only occasional contact and which he was therefore easily able to recognize. The major or unfortunate allergic was, as is observed in allergic practice, sensitized to substances with which he came into frequent or constant contact and therefore could not recognize them. More than 50 per cent suffered from minor allergy but all questionable cases were classed as nonallergic. The total figure is therefore conservative.

These statistical findings are confirmed in a measure by the observations of Rowe[11] who found that 35 per cent of a homogenous student population gave positive allergic histories; of Harkavy[12] who, using only three allergens, found positive skin reactions in 38 per cent of a group of general medical ward patients; and of Rackemann and Simon[13] who using nine test allergens found positive reactions in 50 per cent of presumably nonallergic persons.

5. *The question should no longer be, "Why do some persons become allergic?" but rather, "Why are not all persons allergic?"* If over 60 per cent of the population, the majority, have or have had some form of allergy, severe or mild, then allergy becomes the rule. The so-called normal case becomes an exception, and it is the latter which then requires explanation.

I[14] have stated (1934), "The probability is that the development of sensitization to foreign substances is almost a normal physiologic function, and that if all of us were to live long enough, 100 per cent of the population would at least develop minor allergy."

6. *All persons possess the potentiality of becoming allergic, the susceptibility varying only in degree. It seems probable that in any population, the degree of susceptibility to the development of allergy varies from 100 per cent to zero per cent according to a mathematical formula, depending upon individual variances in susceptibility.*

Spain and his collaborators[15] find that under equal conditions of exposure the percentage of adult human beings susceptible to poison ivy or poison oak varies as the logarithm of the concentration of the irritant applied. This is similar to the response to drugs and other physiologic stimuli in general, in agreement with the Weber-Sechner Law. We may simplify these conclusions somewhat as follows. A given percentage of persons will give positive reactions

to patch tests with 1/1,000 dilution of ivy extract. If those who failed to react are now tested with 1/100 dilution, the same percentage will be found to react. If those who fail to react to the 1/100 are tested with 1/10 concentration, the same percentage will be found to react.

This could be interpreted as indicating that, provided the concentration could be made high enough, all people would react to *Rhus toxicodendron*. All could be made susceptible but with varying degrees of resistance thereto. There is evidence that this is true of other forms of contact dermatitis.

Stewart and Cormia[16] produced nickel dermatitis in guinea pigs, constantly, following cutaneous application. They found that the lesions were similar in every respect to those described in man as nickel dermatitis. The intensity of the reaction was in direct proportion to the concentration of the solution used.

From this we could conclude that, given sufficient concentration and enough exposure, nickel dermatitis can be produced in 100 per cent of instances. This corresponds with the early observation of Walthard (1926) that from 41 to 100 per cent of workers in the Swiss nickel industry developed nickel dermatitis. There was an incubation period in these cases of from fourteen to twenty-one days. Steiner observed positive patch reactions to nickel in 50 per cent of cases of neurodermatitis.

Schittenhelm and Stockinger state that all workers constantly exposed to nickel salts eventually develop eczema. Apparently the degree and concentration of exposure play a great part. Jadassohn remarks that nickel eczema is common in large factories and only occasionally observed in small nickel shops.

These findings correspond to those noted by Spain et al. in ivy poisoning. Bloch[17] has made observations on primula sensitization bearing out the same point. Normal, nonallergic persons were found rarely sensitive to primula, but if the concentration of the antigen was increased, he was able to overcome this constitutional resistance, producing primula sensitization in nonallergic individuals.

Stewart and Cormia remark that sensitivity to chemicals is more easily developed when the exposed individual has a hyperirritable type of skin which develops multiple sensitivity on only occasional contacts.

These observations all tend to confirm the premise which I have already stated, that in dermatitis, even nonorganic dermatitis such as to nickel; in contact dermatitis of the rhus type; and probably also in frank allergy or atopy, it is possible to sensitize 100 per cent of individuals, depending upon the degree and length of exposure. Some individuals become sensitized easily, while others become allergic only in spite of great resistance. There are all gradations between the two extremes, and these gradations can probably be expressed mathematically.

In making this statement I do not mean to imply that there are not other as yet ill understood factors which determine the substance to which one will become allergic, given comparable degrees of exposure.

While the experimental findings deal with nonprotein sensitization the cumulative evidence strongly suggests a similar situation with regard to protein sensitization.

7. *The nature of the allergen plays a part.* It has been claimed that there is a fundamental difference between experimental anaphylaxis and human allergy in that human beings can be sensitized to allergens, only with greatest difficulty or not at all; that when sensitization does occur it appears to be entirely spontaneous and probably associated with hereditary predisposition.

It is quite true that Brunner[18] found that he could not easily sensitize individuals to pollen extract or orris root even after repeated injections. On the other hand he sensitized to ascaris extract with no difficulty.

Jones and Mote[19] found no difficulty in sensitizing human beings to rabbit serum. Simon and Rackemann[20] experienced similar success with guinea pig serum, whether administered through the skin or applied to the nasal mucosa. As a matter of fact the ease with which human beings may be sensitized to foreign serum has been in evidence for many years. The only trouble has been that we have not realized it. The majority of persons who receive therapeutic horse serum develop serum sickness, evidencing sensitization. Hooker[21] has shown that toxins given simultaneously increase the tendency. Twenty-seven per cent of cases receiving toxin-antitoxin subsequently developed positive skin reactions to horse serum. Gordon and Creswell[22] found that 74 per cent of individuals receiving serum who had previously received toxin-antitoxin, gave serum reactions. Forty-three per cent of those who had previously received therapeutic serum (not toxin-antitoxin) reacted after a subsequent serum injection. Tuft[23] found that 28 per cent of children receiving diphtheria toxin-antitoxin became allergic to horse serum.

These observations support my contention[10, 24] that the average person or animal may be sensitized more easily to a foreign protein or substance with which he establishes only occasional contact than to one in which the contact is relatively more constant.

It is difficult to sensitize man to foods which he eats frequently, to feathers, orris root, pollens, house dust—those things to which he is relatively frequently or constantly exposed. Only the 10 per cent who are most highly susceptible to the development of the allergic response become sensitized to common allergens. Those less highly susceptible are more likely to react to proteins which are much more foreign to their economy. This forms the basis of differentiation between the major allergic and the minor allergic.

It is interesting to conjecture that, had the early experiments leading to the discoveries in anaphylaxis been made with substances to which the animals were constantly exposed, the results would have been far different. If guinea pigs eating celery had been injected with celery protein there probably would have been as much difficulty in sensitizing them as occurs when human beings are injected with orris root or pollen extracts. Indeed, it has already been shown that it is as difficult to sensitize animals to pollens as it is to sensitize human beings. If dogs eating beef had been injected with beef extract rather than the extract of sea anemone with which they had never experienced former contact the results might have been different.

In this way the nature of the allergen plays a part in determining sensitization. Let us assume that among human beings there are all degrees of suscepti-

bility to the development of allergy, from those highly insusceptible to the last 10 per cent, who are very susceptible. The intermediate group, represented in my series by the so-called minor allergies, becomes allergic only to those substances with which they establish occasional contact. In the case of proteins these are unusual proteins, proteins to which the individual has not become acclimated. Among the foods this includes such as onions, cabbage, tomato, strawberry, shellfish, and the like.

The middle group, the minor allergies, do not appear to become sensitized to frequent contactants. This is analogous to the observation of Wells[2] who found that young guinea pigs bred from mothers fed on oats could be shown to be highly sensitive to oats, when this food was eliminated from their diet. If they were fed on oats they acquired immunity thereto. But those with an extreme susceptibility to allergy become allergic even to those foods with which they come in frequent contact. Indeed, they are especially likely to do so. This does not mean that they do not also become allergic to the occasional contactant. As a matter of fact in my experience they do so in the same degree and frequency as do the minor allergies. The difference is that in addition to becoming allergic to occasional contactants they also become allergic to frequent contactants.

We do not yet know why a person will develop sensitization to one allergen and not to another, assuming the same frequency or intensity of exposure. There is much that we can assume. We can assume an abnormal permeability of the gastrointestinal tract at some particular time which will predispose toward sensitization. We can assume intercurrent illness. We can accept the evidence that certain foreign substances, such for example as ascaris, are much more likely to produce sensitization than are others, possibly on account of some curious factor in their chemical make-up. We can assume any number of nonspecific factors which might predispose toward sensitization. We can recognize the observations of Walzer[25] and his collaborators, demonstrating that food allergen is normally absorbed through the gastrointestinal tract and transported by the blood in a state still sufficiently like its original so that it can be identified by biologic test (passive transfer). The fact remains that there is a difference between parenteral injection of the foreign protein and the normal digestion, and absorption of the same. Even though it may not be broken down into its constituent amino acids before absorption and even though the foreign protein may in some degree maintain its identity following absorption, the fact remains that only occasionally does it cause sensitization. Digestion must therefore have produced sufficient changes so that there is a difference between the antigenic capacity of parenterally introduced native protein and the same protein after digestion.

In any event, there is much that we do not know as to why one becomes allergic to one substance and not to another. The evidence so far would indicate that a protein or other substance to which one has not been customarily exposed is more likely to produce sensitization, and that among those who are unusually susceptible, the more intense or the more constant the exposure, the more likely is one to develop sensitization.

8. *Inheritance probably plays a part in the allergic predisposition.* This scarcely needs further elucidation. The evidence amassed regarding the inherit-

ance of the allergic tendency appears incontrovertible. Undoubtedly children of parents both of whom are allergic are more likely to manifest allergic symptoms in greater proportion and at an earlier age than children of parents only one of whom is allergic and even more so than children, neither of whose parents is allergic.

Nevertheless it is of interest that I[6] have observed in a series of 100 cases studied for minor allergy that the allergic inheritance is equally heavy in those classified as nonallergic as in those classed as minor allergies. It is only in the major allergies that the inheritance is more pronounced.

Discussion.—I am not alone in the belief that experimental anaphylaxis and clinical allergy represent a fundamentally identical phenomenon. Many writers have expressed the same idea. Bronfenbrenner[36] has very recently presented a most comprehensive and convincing review of the subject, in support of his belief that there is no fundamental difference. Zinsser has written, in his volume *Resistance to Infectious Diseases*, as follows:

> The obvious analogies of many human conditions such as asthma, hay fever, drug and bacterial idiosyncrasies to protein anaphylaxis in animals led, early in the development of this subject, to attempts to elucidate the relationships by clinical and experimental investigations. The difficulties of such researches were, however, many and it became advisable, as trellises for speculation and experiment, to construct tentative classifications of the different forms of hypersensitiveness, based chiefly upon the antigenic nature of the responsible substances and the demonstrability of an antibody mechanism by success or failure of passive transfer. Doerr and Coca particularly established divisions of the subject which we then held as too rigidly conceived. Coca laid particular stress upon the separations he believed enforced by the apparently nonantigenic nature of some of the most characteristically allergenic substances and by an exaggeration (in our opinion) of the importance of heredity as opposed to sensitization by previous contact. He was hampered in his reasoning by gaps in our knowledge—bridged, since then, by the discovery of partial antigens, by the demonstration of intrauterine and intestinal spontaneous sensitization of man and by the recent recognition of the importance of homologous as opposed to heterologous passive transmission. At the present time most workers who have given the subject serious thought agree in fundamental principles, though in regard to serum sickness and a few other conditions diversity of opinion still prevails.

Evidence has been presented in the preceding pages supporting the contention of Rackemann and myself that the allergic and nonallergic individuals are fundamentally alike in their reactive capacities.

If these two premises are correct, it becomes obvious that a theory which attempts to explain the manner of the allergic response should correlate the findings of experimental anaphylaxis with those observed in clinical allergy and with normal physiologic responses. An adequate theory must recognize a denominator common to all three groups. Such a theory must therefore be broader and more generally inclusive than those which have been heretofore proposed. The theory must recognize a mechanism common to all three groups in which the group differentiation is not based on fundamentally different reactive processes.

Allergy must be studied from a much broader point of view than heretofore. I believe that allergy does actually represent a much broader group of phenomena than that of protein sensitization to which it was at first assigned. Just as the earliest experiments in protein anaphylaxis were the most spectacular and

therefore received chief attention, so also the *clinical* observations on protein sensitization were the most spectacular in this field. But, by now, nearly all will agree, I am sure, that clinical allergy involves much more than protein sensitization.

Since the earliest work dealt with proteins, and since the early theories were expressed entirely in terms of protein poisoning, it has been very difficult for many to overcome the mental hazard involved in the acceptance of a conception of nonprotein allergy.

In the present theory I go even farther in this direction by explaining phenomena such as physical allergy and psychogenic allergic reactions which have not hitherto been adequately fitted into the picture of the allergic response, and presenting the entire group of phenomena as a variant of the normal processes of immunity or protective adjustment toward one's environment.

In the years that have elapsed since the development of the original theories explanatory of anaphylaxis, there has been developed such a maze of conflicting and confirmatory laboratory observations that a clear interpretive perspective has become difficult.

I feel, however, that enough experimental material has been accumulated to justify a philosophic approach based upon these observations. The theory herein is presented as such but with emphasis placed on the fact that it is based on the cumulative experimental and clinical researches of the last quarter century.

II. THE ALLERGIC RESPONSE IS BASED ON AN INTEGRATED PURPOSEFUL PHENOMENON

9. *A dominant requirement of all life is that it maintain adequate adjustment to its environment.* Primordial life, whether purely chemical or particulate, as exemplified by the ameba or possibly the phage, depended upon a narrow margin of chemical and physical environmental factors for its continued existence.

The simple cell aggregates worked out communal methods of protection against deleterious environmental influences. The simplest and undoubtedly one of the earliest was in the protective covering of specially differentiated cells.

In man we find an intricate but withal correlated mechanism of protection against extrinsic factors. This protective system includes the skin; mucous membranes; ciliated epithelium; hairs on the body, in the nostrils, in the ears; the turbinates, uvula and epiglottis; the digestive juices; leucocytes; opsonins and antibodies. Among the more obviously protective reflexes we might mention blinking, the pupillary reaction to light, sneezing, coughing, the gag reflex, vomiting, diarrhea, smooth muscle spasm and the coordinated protective reflexes of voluntary muscles.

Deleterious influences against which the body must protect itself include physical factors such as trauma, extreme changes of temperature, intense light, electricity, ultraviolet, x-ray, radium, short wave radio, chemical factors such as acid, alkali, drugs, arsenic, paraphenylendiamine, and biologic factors such as infectious agents, toxins and foreign proteins.

10. *A certain degree of acclimatization is possible by which increased tolerance for deleterious extrinsic factors may be established.* While there is some degree of natural acclimatization to atmospheric factors, to poisons, repeated

low-grade injury (callouses), and other extrinsic factors, nevertheless this environmental adjustment has rather narrow limits. The morphine addict acquires tremendous tolerance for the drug, but he may still be poisoned with morphine. Our continued existence on this planet depends upon the continuation of an optimal temperature range which is not great. It seems quite probable that many of the species of plants and animals which have ceased to exist have done so because they were unable to acclimate themselves to deleterious environmental influences.

One of the simplest examples of normal increased tolerance is that of adjustment to changes of temperature. The first cool spell in the winter seems colder than a much more pronounced temperature drop later in the season, when one has become adjusted. The first hot days of summer are more enervating than those of midsummer. A person from the temperate zone who moves to the tropics finds that he cannot accomplish as much productive work as formerly until after he has been a resident in the tropics for some months and has become acclimated. This question of acclimatization is, as has been brought out by Duke,[26] an important one in the production of physical allergy or hypersensitiveness to heat or cold.

The simplest heat sensitive individual according to Duke is the one who has allergic symptoms only on extremely hot days. Slightly different is the person who has symptoms earlier in the summer but not in midsummer because by then he has become adjusted. Still different and more difficult to recognize is the patient who tolerates midsummer temperature but not a sudden increase, even though the increase be to a temperature which is not as high as that of midsummer. This is the person who experiences symptoms after leaving an air conditioned, cooled cinema. The reverse applies to the cold sensitive individual. Where the hypersensitiveness is manifested more to changes of temperature than to the actual degree of temperature, we find curious situations. Thus the heat sensitive individual may have symptoms only in midwinter when going into a heated house. He cannot tolerate a change from 20 above zero to 70 even though during the summer he had no symptoms at 80. In the summer he had become acclimated. In the winter the change was too sudden for acclimatization. In the same way the cold sensitive individual according to Duke may have symptoms only in the summer time. He adjusts himself to winter temperatures but when in the summer he enters an air conditioned building the sudden drop overthrows his balance.

11. *Complex organisms such as man have built up a complicated system of protective agencies. The allergic response is primarily a protective reaction.* The normal protective mechanisms have been discussed in Section 9. When a noxious substance enters the nose its removal is accomplished by sneezing and the secretion of mucus. The cough, smooth muscle spasm, and increased bronchial secretion of asthma may be looked upon as an attempt to remove a supposed foreign body. Asthma may develop for the first time in connection with a tumor growth in the lung. This is often true asthma and may be relieved by adrenalin or ephedrin. It represents a physiologic reaction, an attempt to remove a foreign body from the lungs. Prompt vomiting which sometimes follows the ingestion of an allergenic food is again a protective response, as is the hyperperistalsis

and diarrhea associated with mucous colitis which often follows the ingestion of an allergenic food which the stomach has not repelled. The serous exudation of a contact dermatitis represents an effort to wash away the noxious substance. Lichenification in chronic dermatitis indicates an effort to establish a protective thickening of the skin at the point of contact. Urticaria and angioneurotic edema which involve internal structures probably to nearly as great an extent as they do the visible integument manifest an effort to dilute the allergenic substance in the tissues, thus protecting the living cells.

12. *All allergic manifestations are correlated. They are purposeful reactions. They are pathologic exaggerations or perversions of a normal physiologic function, that of protecting the body against deleterious environmental factors.*

There is abundant indirect evidence indicating a functional connection, either through the nervous system or endocrine system or both, between the various protective tissues or, better, immunity organs, such as the skin and the mucous membranes. Phillips[27] for example believes that pollen hyposensitization can be accomplished more effectively with intracutaneous therapy than with subcutaneous. The fact that the skin reacts positively to a substance such as pollen which causes symptoms on the mucous membrane but not on the skin is further evidence. It seems reasonable to assume some controlling mechanism which integrates the immunity response or protective response of the skin, mucous membranes, glands, smooth muscle, leucocytes and antibodies.

An example might be found in the person who has attacks of diarrhea following therapeutic pollen injections. But here the intestinal reaction does not accomplish the desired purpose. The reactive mechanism is at work but not with effective accomplishment. This brings us to the next point.

13. *The clinical allergic response sometimes manifests itself as a purposeful reaction, purposelessly executed.* The person sensitive to house dust who has asthma from inhaling this allergen is experiencing a purposeful allergic response. It is true that the dust cannot be completely removed in this way and the symptoms therefore continue but the purpose of the symptoms is obvious. The baker with asthma from sensitization to inhaled wheat is another example. But when a wheat sensitive person develops asthma following the ingestion and enteral absorption of bread, the respiratory reaction can scarcely be termed efficacious. In this instance the protective mechanism is in action but is applied through the wrong agency. The reaction is not coordinated.

14. *When the noxious agent acts from within, the same protective mechanism is set in motion. However, in the absence of an external localizing stimulus, the reaction may manifest itself in any or all of the protective tissues or fluids.* The economy of the human body is so arranged that certain tissues serve certain functions. It is supererogatory to detail the various functions, but I would emphasize that when that of protection has been assigned to certain portions of the body the other body cells lose this ability in great measure. Their functions are intrinsic and in a measure much more elementary. For some reason as yet not clearly understood, if the internal tissues or cells come into contact with a foreign protein a certain reaction occurs which, after a preliminary incubation period, makes that protein highly poisonous. The prevailing theories of anaphy-

laxis have attempted to explain why a foreign protein parenterally introduced, as through a hypodermic needle, becomes poisonous. The present discussion offers nothing new in this regard. Since the Ehrlich hypothesis of antibody formation is the one most generally accepted at the present time, and possibly the most easily comprehended, we can accept it for this discussion. Suffice it to say that a foreign protein, on second entry into the body, becomes highly poisonous. This has also been shown to be true for some nonprotein substances.

As long as there is a clearly defined external point of contact, the reaction usually takes place in that neighborhood. This is exemplified in the dust asthmatic mentioned above. To mention a rather crude example, if, in a large city with several fire departments, a fire breaks out in a certain locality, telephone communication speedily sends the equipment from one of the engine houses to combat the conflagration. But, assume a large fire in the center of the city. An automatic system sends a general alarm to all departments but the automatic system is not working perfectly and no definite information is given as to the location of the fire. The engines will dash hither and yon to the several more probable places. This is the situation when the reaction occurs within the body rather than at localizing areas in contact with the environment. When the reaction takes place within the body it may therefore manifest itself by asthma, urticaria, colitis, migraine (localized urticaria or angioneurotic edema), generalized edema (acute anaphylactic shock), or by a combination of two or more of these symptoms.

The reaction is protective but the mechanism does not know which area to protect. Certain areas appear to be more reactive than others.

The tropic importance of a contact factor is well exemplified in the work of Auer,[28] of Valy Menkin[29] and of Seegal, who have shown in anaphylactic shock that if a given area is first irritated chemically or by local infection, antigens accumulate in greater concentration in this area and the local reaction is decidedly more pronounced.

This possibly explains some of the allergic reactions that cannot be attributed to the action of the protective mechanism. It is a matter of common experience that patients with true bile tract infections often find that certain specific foods precipitate typical gallbladder attacks. In this case the allergy is an exciting factor, probably attributable to concentration of antigens or reagins at the site of local infection. The same may be true in cases of peptic ulcer.

One might argue that an inhaled substance should always produce respiratory allergy or a substance ingested should always produce gastrointestinal allergy. It has been demonstrated, by the work of Sulzberger and myself,[30] that foreign allergens may enter the circulation through the lungs or respiratory mucosa, causing no reaction therein but producing remote lesions in the skin. Certain of the protective tissues may be more reactive than others. An allergenic food may produce gastrointestinal symptoms or after absorption it may be responsible for asthma, migraine, or so-called neurodermatitis. The same explanation holds.

I realize that Walzer and his associates have demonstrated that foods, when eaten, are absorbed into the blood in a condition still sufficiently like their native state so that they can be demonstrated as having reached the skin by the

Prausnitz-Küstner technic. But they are not still native proteins, since this phenomenon is quite different from that which follows the parenteral introduction of foreign protein with consequent sensitization. The enteral introduction of protein in the form of food may be followed by absorption of a substance which is still identifiable as similar, but it has nevertheless already been changed enough so that it does not usually produce sensitization.

The hypothesis herein presented does not explain why or under what circumstances an individual becomes allergic to a definite foreign protein or other substance. This question still awaits solution. We speak with ease of abnormal absorption associated with gastrointestinal upset, of unusual or prolonged exposure, but the final secret of why one becomes allergic to one allergen and not another is yet unsolved. My attempt has been, rather, to explain what happens after sensitization has occurred, and why the clinical symptomatology is such as it is.

15. *Certain organs or tissues may be locally sensitized, or more highly reactive than others.* This is an acceptance of Coca's[1] theory of shock organs or shock tissues. If a child's first manifestation of food allergy is asthma the respiratory protective mechanism has become either locally sensitized or unusually reactive. We cannot distinguish which of these two possibilities is correct. If a person has had respiratory allergy for years, reacting with asthma, and later becomes sensitized to a food which likewise causes asthma, we might conclude that this indicates a hyperirritability of the respiratory mechanism. But when a specific food causes migraine constantly to the exclusion of urticaria or angioneurotic edema, we must consider a shock tissue, locally sensitized.

We must therefore add the possibility of a local predisposition, to the general picture as described above.

16. *The vagus autonomic system may play an integrating part in the constitutional allergic response.* Vagotonia or vagosympathetic dystonia has for years hung in the background of the allergic picture. I would emphasize that the entire system of cranial nerves is intimately connected with the mechanism of protection against deleterious environmental influences. Pupillary contraction, ocular movements, the senses of taste and smell and of hearing, the sense of equilibrium, swallowing or its absence, the muscular activities of the larynx, vomiting, and the respiratory activities controlled by the vagus, all deal more or less intimately with self-protection. When we recall that the autonomic system includes innervation of the descending colon and the rectum as well, but does not include the small intestines, we see further reason for including the autonomic system in the protective mechanism. The theory of vagotonia as an important factor in allergy is therefore very easily fitted into the mosaic of the hypothesis here presented.

17. *Mental or emotional factors may precipitate the allergic response.* This is seen especially in urticaria but occurs also in asthma, migraine, and less frequently in other allergic diseases. There have been many reports of so-called neurogenic urticaria in which the victim, unable to solve his or her domestic problem, disagreements within the family and the like, reacts with urticaria. This is again an expression of environmental maladjustment. Protein need

play no part here. The reactive mechanism, possibly activated through the autonomic nervous system or the endocrine system or both, receives its stimulus from the higher nerve centers, but the site and basis of the reaction are explained in the same manner as in frank allergy.

18. *The endocrine system probably plays some part in the protective mechanism.* The action of suprarenal cortex in preventing anaphylactic shock[31] and of epinephrine in lessening its severity when it has occurred should be mentioned. It should also be recalled than Cannon[32] has elaborated a theory concerning the function of the adrenal secretion in which he gives it a most prominent place in the protection of the individual against deleterious environmental influences. Epinephrine is a "fight or run" hormone. It speeds the heart, raises blood pressure, relaxes bronchial musculature thereby facilitating respiration, diminishes the blood supply to the skin while increasing that to the internal organs thereby giving additional nutrition to the musculature, discharges glycogen into the circulation, providing an increased blood sugar content for utilization if necessary. Whether the environmental influence calls for combat or for flight the physiologic response to increased epinephrine secretion has provided optimal conditions.

The objection might be raised that epinephrine lessens all of the so-called protective activities which we have described. But it should be borne in mind that the allergic response is a disorganized or disoriented one. We might speak of it as out of proportion to the intensity of the stimulus. It becomes obvious that the adrenal secretion controls the intensity, character and direction of the response. Physiologists have studied the glycogenolytic activity of epinephrine, its action in relaxing smooth muscle spasm, in raising blood pressure and increasing the pulse rate and the like, but there is much that we do not know regarding the effect of this secretion on the tissue cells in general. Epinephrine serves as a balance wheel or a governing factor, controlling the intensity and direction of the allergic reaction. It coordinates it and tends to keep it within normal limits.

19. *The allergic reaction represents a response to an environmental maladjustment.* Richet, visualizing a purely experimental phenomenon, and attempting to explain it in terms of immunology, coined the term *anaphylaxis,* indicating the absence of protection as contrasted with prophylaxis or *favoring protection,* as observed in the development of immunity. Victor C. Vaughan and Wheeler[33] (1907) were the first to state their belief that the fundamental processes at work in immunity and in anaphylaxis were identical. This concept has been generally accepted.

It is at once obvious that in the theory herein presented, the reactive bodies, which are in essence the protective mechanism of the human body, are the same in allergy as in immunity. In the processes of immunity they react with maximum efficiency, thereby protecting the body as a whole. In clinical allergy they do not fail to react as would be indicated by the term anaphylaxis, but they react abnormally. The reaction is, as I have said, disoriented, disorganized. A more appropriate term would be *dysphylaxis* (difficult protection) or *dysphyl-ergy* (labored reaction of protection). The reaction is of normal type, but apparently uncontrolled.

20. *So-called nonspecific therapy or shock therapy, when efficacious, exerts its beneficial effect by stimulating the reactive mechanism to more effective response.* It is a matter of common experience that an allergic individual often loses his allergic manifestation following an acute illness such as pneumonia, typhoid fever, acute appendicitis, any surgical operation or, indeed, simple anesthesia. The same improvement sometimes follows foreign protein therapy such as intravenous typhoid or colon bacillus vaccine, peptone injections, or even the subcutaneous injection of so-called specific or nonspecific vaccine.

It is probable that all of these stimulate the immunity mechanism, the same mechanism which is responsible for the allergic response, in such a way as to make it more effectively responsive, more efficient, at least for a time. Eventually, however, it again loses its acquired effectiveness and allergic symptoms return.

III. THERE ARE DEGREES OR TYPES OF RESPONSE TO HARMFUL ENVIRONMENTAL CHANGES

21. *Normergy: the normal response.* It would be hazardous indeed to attempt to present a new classification of the phenomena of idiosyncrasy, since there are already so many which use the same terms but interpret them entirely differently. However, there are four terms already in use, although used differently by different writers, which so clearly fit into the hypothesis herein presented that I venture to express my own interpretation of them in illustrating my concept of the manner in which a living body reacts to environmental influences.

The normergic is obviously the person who can always adjust himself satisfactorily to the usual range of deleterious environmental influences. Extremes of temperature and humidity, dietary and inhalant factors, even infection, are well tolerated. Exposure to infection rapidly produces an adequate immunologic response.

Some observers have stated their opinion that allergic individuals are especially resistant to infection. While this statement has not received universal acceptance, it is interesting to speculate on a hyperactivity of the immunity mechanism which would account for this. While the allergic reaction is incoordinated in its clinically recognizable responses, it is nevertheless a rather violent or intense reaction, and it is possible that it is as intense in its serologic and tissue immune response as in its nasal, bronchial, or dermal response. This might result in some increased resistance to infection. On the contrary we should bear in mind Rackemann's observation previously mentioned, that he was unable to find any difference between allergic and nonallergic individuals as regards antibody production.

22. *Allergy; abnormal response to deleterious environmental influences.* The simplest manifestation of an allergic reaction to environment is observed in physical allergy. The person who responds to extreme heat or cold, sudden temperature changes, to ultraviolet radiation or to effort with typical allergic symptoms, such as asthma, vasomotor rhinitis, urticaria, is an allergic individual. His reactive mechanism is broken down and he responds with a misdirected or perverted protective reaction.

The work of Petersen[34] who has shown that deaths from asthma in Chicago are much more likely to occur during a polar infall, occurring during changes in cyclonic fronts, irrespective of the immediate allergic etiology of the asthma, indicates the importance of environmental factors. Apparently some allergic individuals as well as nonallergic tolerate sudden meteorologic changes better than others.

23. *Hyperergy; exaggerated normal reaction to environmental factors.* This may or may not be an intermediate stage between normergy and allergy. I have gained the impression in my studies, that allergic persons are more likely to be hyperergic to drugs and the like than are normergies. However, I have made no statistical analysis in this regard.

The person who reacts to extreme degrees of heat, not with asthma or urticaria, but with heat prostration, is hyperergic. He reacts in a normal way, but more violently than the normergic. I would interpret most of Duke's cases of effort syndrome as hyperergic rather than allergic. The person who has adjusted himself to his daily routine may, when inducted into army service and exposed to intensive physical exertion to which he is not accustomed, react with those symptoms which are today well known. He experiences palpitation, tachycardia, tremor, attacks of syncope and the like which are grouped under the designation "effort syndrome," or "soldier's heart." These are the reactions which one normally experiences to unusual or severe effort but which some people, hyperergic, experience following a degree of effort which causes no symptoms in normergics.

The person who develops urticaria from belladonna is allergic. The one who, following normal dosage with belladonna, experiences dryness of the mouth, dilatation of the pupils, or, in extreme cases, atropine convulsions, is hyperergic. Those who sunburn easily are hyperergic. Those who develop asthma following exposure to ultraviolet rays are allergic.

24. *Anergy; absence of reaction.* Tissue cells appear to be unable to react at all to certain noxious and deleterious substances with which they come in contact. This includes simple poisons such as bichloride, phenol, acids, alkalis, and the like. There is no protective mechanism.

There is no sharp differentiation between these four groups. Workers in tar develop what is known as tar dermatitis. Some do it more easily or sooner than others. These might be classed as hyperergic. But, given sufficiently long contact, nearly all such workers develop dermatitis. This of course will include the normergics, and there is no recognizable division between the two groups. Given sufficient exposure probably 100 per cent will eventually develop symptoms. The reaction is primarily a protective one but manifests itself in an abnormal way and might therefore be called allergic. Here again there is no clear-cut point of cleavage between the groups.

If we speak of allergy as a pathologic exaggeration of a normal physiologic response, we might well speak of hyperergy as a normal exaggeration of a normal physiologic response.

In the same way anergy cannot be clearly differentiated. Bichloride of mercury applied to the skin in an allergic individual may produce a contact

dermatitis. It is when this type of chemical comes in contact with the internal tissues, with no external points of contact, as after parenteral administration or sometimes after enteral administration, that anergy manifests itself. The tissue cells themselves appear to have no protective ability although with some of these substances tolerance can eventually be acquired through repeated small dosage.

IV. DISCUSSION

The theory herein presented explains the allergic response as an integrated reaction complex, fundamentally protective in nature, but defective in execution since it lacks coordination and a directing influence. It is, in essence, a manifestation of environmental maladjustment. This is in harmony with the idea recently expressed by Gay,[2] "It is our thesis that the ultimate explanation and prevention of a disease depends on ascertaining its external cause. * * * Not only diagnosis but cure and prevention depend on knowledge of the originating impulse. This impulse, animate or inanimate, is the essential element to discover, and when discovered has invariably been found to be external. * * * We have already expressed our prejudice in favor of the eventual explanation of all disease on a basis of external causation. * * * The cause of disease remains predominantly external."

Given sufficiently heavy exposure (contact, meteorologic, food, infectious), 100 per cent of the population is capable of responding abnormally, either with hyperergy or allergy. There appear to be all grades from those who are extremely susceptible to those who are very insusceptible.

Two outstanding factors appear to play a part in determining susceptibility. The first is heredity. This represents either a congenital inability to adjust or a congenital predisposition to maladjust. Such a person is often spoken of as vagotonic. The function of the vagus autonomic system and its relation to allergic manifestations has been discussed.

The second factor is that of the nature of the exciting factor, whether it be protein or not, and the intensity and chronicity of exposure thereto. The mildly allergic individual may become sensitive to a relatively new or strange allergen with which he comes into only occasional contact. The person with high susceptibility may become sensitive to these and also to those substances with which he comes in frequent or chronic contact.

The theory herein proposed very materially simplifies our understanding of allergic therapy. The simplest way to circumvent deleterious reaction to a harmful environment is by avoiding this environment. This is obviously the principle of avoidance in allergic therapy. But where the noxious influence cannot be avoided, acclimatization may be attempted, by exposure of the tissues to constant or repeated contacts. This is the basis of hyposensitization or desensitization and accomplishes results in the same manner that acclimatization to deleterious temperature changes produces increased tolerance.

The process of hyposensitization is in essence a process of acclimation.

This principle places perennial pollen therapy on a rational basis.

The question arises as to why minor allergic individuals become sensitized only to occasional contactants while major allergics display their outstanding idiosynerasies to frequent or chronic contactants. We have already mentioned the work of Wells who found that guinea pigs born allergic to oats appeared to desensitize themselves when eating oats but showed clear-cut allergy thereto when placed upon an oat-free diet. It may be that there is as great a tendency to become allergic to allergens to which one is frequently exposed as to those to which exposure is only occasional. The former, however, may very well desensitize by virtue of this frequent exposure, as in the case of the guinea pigs. The minor allergic individual may become hypersensitive to wheat, egg, and milk as easily and frequently as the major allergic, but he fails to manifest symptoms therefrom because he readily desensitizes himself by chronic exposure or acclimatization. The person with an unusually pronounced tendency, the major allergic individual, cannot acclimate himself even with frequent or constant exposure and as a consequence develops symptoms. I would again emphasize that in my experience the major allergic person is also sensitive to occasional contactants, and in roughly the same frequency as the minor allergic. He is fundamentally the same as the minor allergic person in this respect and in addition is unable to acclimate himself to sensitization to frequent contact substances. The minor allergic individual often gives positive skin reactions to substances such as wheat, egg and milk even though these do not cause symptoms. He is allergic but he is acclimatized. This explains many or all of the so-called false positive reactions observed in allergic testing.

If susceptibility to the development of allergy varies from zero per cent to 100 per cent one would expect occasionally to find persons who are allergic to practically everything. Such types although fortunately uncommon undoubtedly do exist. I have had occasion to treat a man who was in the produce business, and therefore came into contact with many unusual foods as well as all of the common ones. He was found allergic to 42 different foods, and when tested by the Prausnitz-Küstner technic with the biologic food groups gave positive reactions to 16 of the 30 test extracts. Rinkel[35] has observed certain intractable asthmatic persons who respond with a positive leucopenic index to practically every food with which they are tested. We have been able to confirm this in our own experience. There might be some question as to whether this indicates that they are actually allergic to each of these foods, but there is no gainsaying that, whether allergic or not, they respond to ingestion of all the foods in an allergic manner. Although the reaction may not be specific it is an allergic type of response.

CONCLUSION

The theory herein described is presented in an effort to clarify our understanding of the manner and meaning of the allergic response and in the hope that, this being better understood, there may be consequent eventual advances in the therapy of the allergic diseases. If the hypothesis contains an element of truth, it should promote investigation in a field which has received too little attention up to the present. Until now chief effort has been given to neutraliza-

tion or counteraction of a specific response to recognized specific allergens. It seems possible that efforts to develop a nonspecific or physiologic means of controlling the perverted, disoriented reaction of protection so that it may become a normal oriented reaction, might actually lead to the discovery of a remedy which will adequately control the response irrespective of the activating cause.

The two lines of approach which from the theory would appear to offer possibilities, deal with the endocrine system, particularly the adrenals, and the autonomic nervous system. Studies in these two fields have until the present been disappointing, but the possibility always remains that, as was true in the case of Banting and Best's discovery of insulin, a somewhat different method of approach may be more successful. There also remains the possibility of the recognition of a new mechanism not identified with either of these two systems.

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LABORATORY METHODS

A CULTURAL METHOD FOR THE DIAGNOSIS OF GONORRHEA EMPLOYING THE DIRECT OXYDASE REACTION*

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IN RECENT years the diagnosis of gonorrhea by cultural methods in addition to demonstration of the organism in smears has attracted considerable attention. Fröhlich and Jordan,[1] Hämel,[2] and Schlirf[3] are among those who have investigated the possibilities of cultural diagnosis of gonorrhea recently. McLeod and his associates[4] have no doubt done more in this connection than any other investigators to date. In addition to this they were the first to introduce[5, 6] the use of the direct oxydase reaction for the purpose of detecting gonococcal colonies in mixed cultures.

To our knowledge, only three reports upon the use of the oxydase reaction in the diagnosis of gonorrhea have appeared in the literature since its inception by McLeod. Price[7] and King[8] in England, and Carpenter[9] in this country, have reported the use of this method with favorable results. McLeod[4] reports excellent results on the use of the oxydase reaction in a large series of cases. These favorable reports suggested the possible adaptation of the oxydase reaction to routine laboratory procedure.

In developing a routine laboratory method for the cultural diagnosis of gonorrhea, the first consideration was a suitable medium. It was desirable that this medium should support excellent growth of the organism, and be of such nature or composition that it could easily be duplicated. North gelatin agar (Difco) was found to possess the above qualifications. This medium was enriched by the addition of 10 per cent sheep blood while hot. This gave a chocolate medium upon which the gonococcus could be grown with little difficulty. The composition of this medium is always constant and comparable results should be obtainable anywhere with its use. The medium was sterilized and stored in 100 c.c. flasks in the refrigerator, and when ready to use was liquefied, the blood added, and the plates poured. In this way a fresh, moist surface for growth was afforded the gonococcus.

The source of material for culture was some distance from the laboratory, and a point of difficulty was encountered when the problem was first begun. The swabs of the exudates were transported to the laboratory where the plates were inoculated. This method proved to be unsatisfactory since the exudate dried rapidly on the swabs. It was noted that the less exposure to drying and lowered

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Received for publication, June 18, 1935.

temperatures to which the material was subjected, the better the possibility of growth. When this fact had been ascertained, a method was devised whereby the plates could be taken to the source of the material, inoculated, and returned to the laboratory without undue exposure. A corrugated paper box large enough to hold several dozen Petri plates was lined well with cotton batting. The plates were put in this box, packed well with cotton, and the box sealed. In this way the plates could be transported to the patients, inoculated, and returned to the laboratory for incubation without any undue exposure. Undoubtedly, however, the best procedure is to have the patient come to the laboratory.

The plates are stroked with the swab containing the exudate, after which they are incubated at 37° C. Colonies grow on this medium within twenty-four hours and are considered mature within from forty-eight to seventy-two hours.

Fig. 1.—Gonococcus in mixed culture on heated blood agar, as usually obtained from the female urethra. Before treatment with tetramethyl-p-phenylenediamine hydrochloride.

The plates are now covered with a freshly prepared 1 per cent aqueous solution of tetra methyl-para-phenylene diamine hydrochloride,* which is immediately poured off. Medium-sized convex and translucent colonies which rapidly turn a bright purple color, are gonococci, if upon microscopic examination they are gram-negative diplococci.

Carpenter† considers the dimethyl para-phenylene diamine superior to the "tetra methyl" compound, believing the latter to be less toxic but staining the medium so deeply that there is frequently difficulty in distinguishing a gonococcus colony.

In the work discussed in this paper no difficulty was encountered in this connection. True, the medium does turn a deep purple color after a few minutes, but there is sufficient time to detect the gonococcal colonies and "fish" them for

*Prepared by Eastman Kodak Co. (Organic chemical division.)
†Personal communication.

transplants and microscopic examination before the medium is dark enough to make the colony indistinguishable.

In the great majority of cases where a positive oxydase reaction was secured, the organism was a gram-negative diplococcus when checked by staining and microscopic examination.

The practical importance of the oxydase reaction in the detection of gonococcal colonies lies in the fact that one can readily observe the presence of gonococcal colonies in a heavily mixed or contaminated culture such as is obtained from the urethra of the female, whereas by ordinary methods this would be a long and laborious procedure.

Fig. 2.—The same plate culture (Fig. 1) after treatment with tetramethyl-p-phenylenediamine hydrochloride. The dark colonies are oxydase positive gonococci.

SUMMARY OF TECHNIC

Medium.—North gelatin agar (Difco) prepared as directed on container. Heated to 75° C. and 10 per cent sheep blood is added, which gives a chocolate medium; allowed to solidify and then inoculated.

Incubation.—At 37° C. for forty-eight hours.

Identification of Gonococcal Colonies.—One cubic centimeter of the dye compound is poured on the surface of the medium to flood the colonies, and is poured off immediately. The gonococcal colonies turn a bright purple color in a few seconds.

RESULTS OBTAINED IN THE CULTURAL DIAGNOSIS OF GONORRHEA IN THE MALE

Males coming to the venereal disease clinic and presenting the clinical symptoms of gonorrhea were examined culturally for diagnosis. The majority of the patients observed were in the acute stage and exhibited purulent discharge. Seventy-seven patients were examined. The results are tabulated in Table I.

TABLE I

COMPARISON OF SMEARS AND CULTURES OF THE MALE URETHRA

NEGATIVE SMEAR NEGATIVE CULTURE	NEGATIVE SMEAR POSITIVE CULTURE	POSITIVE SMEAR NEGATIVE CULTURE	POSITIVE SMEAR POSITIVE CULTURE
22.0%	10.3%	7.7%	60.0%

In Table I it may be noted that in a small number of cases a positive culture was obtained when the smear was negative. In two cases a positive smear was accompanied by a negative culture.

RESULTS OBTAINED IN THE CULTURAL DIAGNOSIS OF GONORRHEA IN THE FEMALE

Females undergoing treatment for gonorrhea at the venereal disease clinic were examined culturally for progress of treatment. The majority were chronic cases of gonorrhea. Fifty-nine patients were examined. The results are given in Tables II and III.

TABLE II

COMPARISON OF SMEARS AND CULTURES OF THE FEMALE URETHRA

NEGATIVE SMEAR NEGATIVE CULTURE	NEGATIVE SMEAR POSITIVE CULTURE	POSITIVE SMEAR NEGATIVE CULTURE	POSITIVE SMEAR POSITIVE CULTURE
52.5%	10.2%	0	37.3%

Positive cultures were obtained in all cases showing positive urethral smears and in six cases showing a negative urethral smear. In no cases were there negative cultures with positive smears.

TABLE III

COMPARISON OF SMEARS AND CULTURES OF THE FEMALE CERVIX

NEGATIVE SMEAR NEGATIVE CULTURE	NEGATIVE SMEAR POSITIVE CULTURE	POSITIVE SMEAR NEGATIVE CULTURE	POSITIVE SMEAR POSITIVE CULTURE
49.2%	32.2%	0	18.6%

Positive cultures were obtained in a considerable number of cases in which the cervical smear was negative.

The data presented in Tables II and III indicate that the cultural method is superior to the microscopic method in the diagnosis of gonorrhea in the female. This was most marked in the examination of the cervical exudates. Smear positive 18.6 per cent; culture positive 50.8 per cent.

DISCUSSION

Cultural methods accompanying physical examination of the urogenital tract furnish an index of cure and greater accuracy in the diagnosis of gonorrhea. The value of the cultural method is further enhanced by the oxydase reaction, which demonstrates the presence or absence of gonococcal colonies in a mixed culture such as is usually obtained from the female urethra. The microscopic examination of all the colonies in such a culture would be a time-consuming and tedious task, whereas by the use of the oxydase reaction the presence of gonococcal colonies may be quickly determined.

The oxydase reaction is not specific for the gonococcus, and similar reactions are given by other members of the genus *Neisseria*. However, such organisms are rarely encountered in the urogenital tract. False positive reactions may be given by *B. coli* and *B. subtilis*, but these organisms are easily distinguishable from gonococci both macroscopically and microscopically.

CONCLUSIONS

1. The medium and technic employed are adaptable to general laboratory routine.

2. To obtain the maximum percentage of positive cultures it is necessary that the specimen be cultured immediately.

3. The detection of gonococcal colonies in mixed cultures is greatly facilitated by the use of the direct oxydase reaction.

4. Cultural demonstration of the gonococcus aided by the oxydase reaction and subsequent staining is superior to microscopic demonstration alone in chronic infection of the female. This is especially noticeable in cultures of the cervical exudates.

NOTE: Since this paper has been submitted for publication Luther Thompson of the Mayo Clinic (J. Bact. **31**: 82, 1936) reports a positive oxydase reaction with *Neisseria catarrhalis*, *Neisseria flava*, and *Hemophilus influenza*. These results emphasize the absolute necessity of a microscopic examination of oxydase positive colonies in all cases.

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ANIMAL GROWTH AND SPACE RESTRICTION*

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NUTRITIONAL studies in progress for several years have revealed that space restriction is a factor involved in the character of growth and development of young animals. In three sets of experiments on young rats maintained on a balanced and adequate basic dietary, it was found difficult to obtain satisfactory growth. After eliminating some factors—good progeny, a complete dietary, freedom from infection, favorable hygiene, adequate sunshine—spatial restriction appeared to be the detrimental factor to growth and development. With this in view the experiment was repeated with another series of animals, maintaining all conditions constant excepting the volume of space occupied per animal.

METHOD OF PROCEDURE

White albino rats of known pedigree stock, five weeks old, were selected for study in small and large cages respectively, each animal having available 120 c. in. space in small cages, 430 c. in. space in the large cage. The cages used were standard make of galvanized wire netting with double bottom. The diet given below was prepared in required amounts for the twenty-four-hour period, and placed in cages mornings; water was added ad lib., weights were taken weekly, and those that thrived were put into the activity cage. The lima beans and potatoes were cooked for three hours at forty pounds' pressure and the other ingredients were added later. These mixtures were prepared on the average of three times a week, kept in refrigeration between 40° to 45° F. and fed daily.

Table I

Dietary Composition

FOOD	WEIGHT	PRO.	CARBO.	FAT	CALORIES	BASIC
Klim	20 gm.	5.2	7.6	5.0	105.0	3.3
Potato	100 gm.	2.5	20.9	0.1	96.9	7.7
Beans (lima)	60 gm.	10.8	39.6	0.9	210.0	24.0
Dextrin	3 gm.	---	2.7	--	17.0	---
Agar	2 gm.	---	---	--	----	---
		18.5	70.8	6.0	428.9	35.0

The groups of animals studied in small and large cages were compared quantitatively from the standpoint of relative activity. The animals confined in small cages were entirely too feeble to be placed in the activity cage and so

*From the Heckscher Institute.
Received for publication, May 4, 1935.

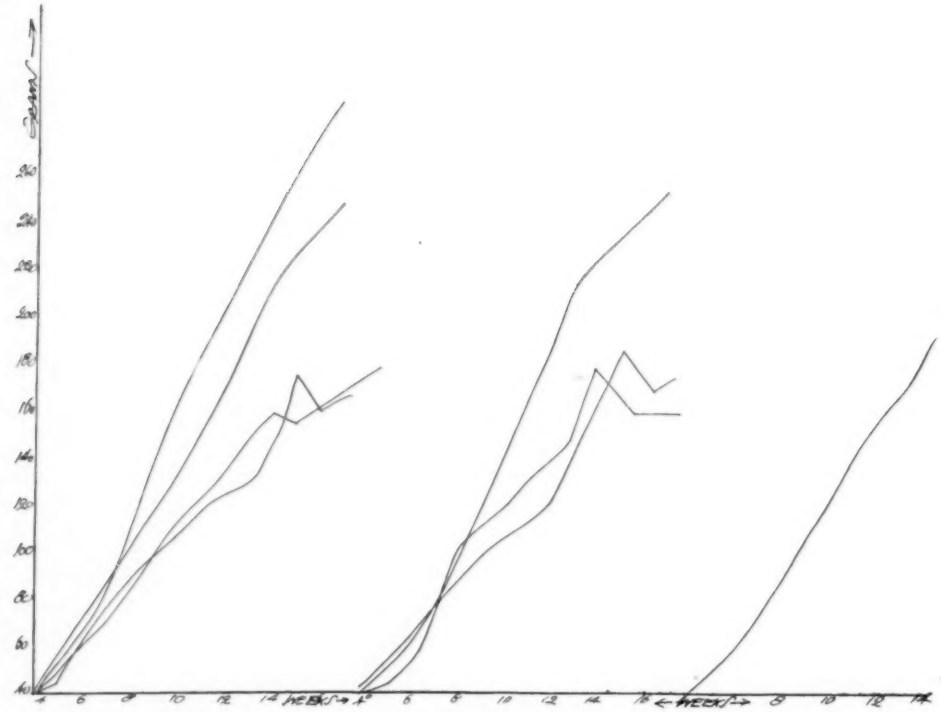

Chart 1.—The growth curves of rats maintained on normal diets without space restriction.

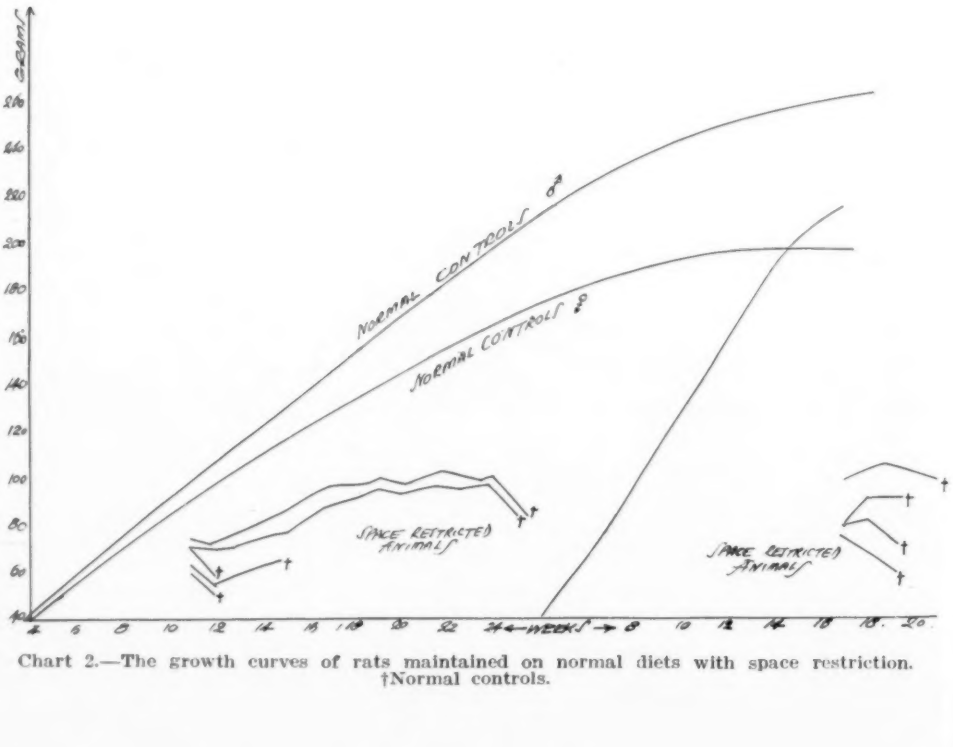

Chart 2.—The growth curves of rats maintained on normal diets with space restriction.
†Normal controls.

only results of the animals in the large cages are given below. Each animal was first confined in the activity cage without freedom and twenty-four hours later the same animal was maintained in activity with voluntary periods of freedom.

TABLE II

ACTIVITY VALUES. COMPARATIVE RESULTS OF ANIMALS ON COMPULSORY AND LEISURE ACTIVITY

RAT NO.	CONTINUOUS ACTIVITY			INTERMITTENT ACTIVITY		
	WT. LOSS	FOOD CONSUMED	QUOTIENT	WT. LOSS	FOOD CONSUMED	QUOTIENT
048	8 gm.	6 gm.	2081	3 gm.	26 gm.	2032
049	5 gm.	12 gm.	4591	6 gm.	20 gm.	1681
050	2 gm.	15 gm.	2158	2 gm.	30 gm.	750
051	6 gm.	16 gm.	2956	3 gm.	30 gm.	3526
052	6 gm.	8 gm.	2641	2 gm.	35 gm.	1810
053	1 gm.	6 gm.	3043	1 gm.	28 gm.	733
054	6 gm.	7 gm.	2203	3 gm.	20 gm.	2262

TABLE III

COMPARATIVE RESULTS OF ANIMALS LIVING IN SMALL AND LARGE CAGES

	SPACE VOLUME PER ANIMAL	RATE OF GAIN	LIFE SPAN	ACTIVITY VALUE PER DAY	NO. ANIMALS PER EXPERIMENT	INITIAL WEIGHT
Small cage	120 c. in.	1 gm.	8 wk.	Feeble	9	71 gm.
Large cage	430 c. in.	14 gm.	18 wk.	2,500 rev.	7	40 gm.

RESULTS

The animals maintained in the small cages occupying on the average a space of 120 c. in. per rat failed to gain weight, grow, or develop consistently. One of them died in the third week, the second in the fifth week, a third was put on another normal diet, died nevertheless in the seventh week. In another series of animals six weeks old, the initial weight averaging to 67 gm., the life span was fifteen weeks with a change in weight of 10 gm. of their initial weight. Another series six weeks old, weighing between 55 and 88 gm., the fourth remaining alone on another normal diet, continued to live. Their average food consumption was 34 gm. per rat per day.

The animals maintained in a large cage, occupying a volume of 430 c. in. per animal, all thrived on the same dietary as those in the small cages. The rats were four weeks old, averaging 40 gm. with an average daily food consumption of 92 gm. per rat. These two groups of animals in large and small cages respectively on the same dietary, showed a striking difference in the character of their growth and development. The animals confined in the small space died within two or three months as compared with those in the large space which continued to live. In a previous communication we have demonstrated that the base forming dietary is conducive to great activity with marked liberation of energy in comparison with other dietary. Space restriction on such buoyancy forming dietary is evidently not favorable for development.

The animals maintained in a spacious environment were further tested from the standpoint of compulsory and leisure activity. The average amount of food consumed was 39 gm. per rat per day, the average loss of weight per rat in the

compulsory group was 5.3 gm. in comparison with the leisure group which was 2.8 gm. The revolutions of the compulsory group were 2,828 in comparison with the leisure group which were 1,706 revolutions. The average of food consumption of the compulsory group was 10 gm. per rat per day in comparison with 27 gm. of the leisure group of rats.

CONCLUSIONS

1. A comparative study of two groups of young rats maintained on a normal base forming dietary revealed that the volume of space occupied was a factor involved in growth and development.

2. The animals maintained in a limited volume of space failed to thrive in comparison with those reared in a spacious environment.

3. The life span of the animals confined in a restricted space was short in comparison with those reared in abundant space.

4. The average food consumption of the animals confined to continuous activity was considerably less than those offered relative freedom activity.

DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

PNEUMONIA, LOBAR: Occurrence of Myelocytes in Peripheral Blood in, Stephen, D. J. Am. J. M. Sc. **188:** 332, 1934.

In 43 unselected cases of lobar pneumonia, the white blood cell response was studied in detail, using both fixed and supravitally stained preparations.

In the majority of patients, small numbers of myelocytes were frequently found in the peripheral blood during the acute febrile period of the disease.

In patients who recovered, a consistent, and frequently striking, shower of myelocytes was observed in the peripheral blood during the period immediately following crisis and lysis.

It is suggested that the postfebrile myelocyte shower may be due to the stimulating effect of nuclear material liberated during resolution of the pneumonic exudate.

PNEUMONIA: Cytology of Pleural Effusion Studied With a Supravital Technic, Scott, T. F. McNair, and Finland, M. Am. J. M. Sc. **188:** 322, 1934.

A supravital technic was used to study the cytology of 53 pleural fluids from 32 patients with pneumococcus lobar pneumonia. The cell types encountered are described. Their occurrence and frequency are correlated with the outcome of the effusion and the course of the pneumonia.

The cellular content of the infected fluids consisted almost exclusively of polymorphonuclear neutrophiles in various stages of degeneration. In uninfected fluids the predominating cells, in the beginning, were active polymorphonuclear neutrophiles, but these decreased in number during the first week at which time monocytes and macrophages appeared in the fluid. Later in the disease, after crisis had taken place, lymphocytes began to appear in these sterile fluids.

Moderate to marked eosinophilia was noted in three cases. This occurred during the third week, or later, after the onset of the pneumonia.

TUBERCULOSIS, Clinical Study of Allergy and Immunity, Karan, A. A., and Danford, V. H. Am. Rev. Tuberc. **30:** 320, 1934.

An attempt to correlate the intensity of the intracutaneous tuberculin reaction with the clinical progress, in a group of 40 tuberculous patients receiving collapse therapy, gave negative results.

The intracutaneous tuberculin test, before collapse therapy was instituted in this group of patients, failed to reveal any correlation between the intensity of the reaction and the type of disease.

Graphs of the successive reactions in each patient did not disclose any typical curve in patients who improved and in those with progressive disease.

ANEMIA: Evanescent Effect of Intratibial Injections of B. Welchii Toxin in Rabbits, Goldwater, L. J., Connery, J. E., and Heimann, H. Am. J. M. Sc. **188:** 339, 1934.

In the authors' search to find a suitable method for assaying the potency of substances effective in the treatment of the macrocytic hyperchromic anemias they attempted to induce an anemia in rabbits by a single intratibial injection of hemolysin-free *B. welchii* toxin. Since the changes in the blood of the test animals were quite evanescent and since the blood picture of the test animals rapidly returned to a condition similar to that seen in the control animals, this method was deemed unsatisfactory for their purposes.

TUBERCULOSIS: Leukocyte Count During Artificial Pneumothorax Treatment and Lung Expansion, Deegan, J. K. Am. Rev. Tubere. 30: 256, 1934.

The Medlar interpretation of blood counts (see below) in cases of far-advanced pulmonary tuberculosis subjected to collapse therapy is a valuable guide in the clinical administration and control of these patients.

TYPES	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS
Septic type, abscess-formation. New tubercle-formation if mononuclears above 9 per cent	Usually above normal. May have leucocytosis or leucopenia	Above 65 per cent	Below 25 per cent	Usually above 8 per cent
Hyperplastic type, new tubercles formed but not undergoing abscess-formation. 30 per cent lymphocytes = healing tendency	Normal limits	Below 60 per cent	25 per cent or more	Above 10 per cent
Nonseptic type	Never over 10,000	Lymph per cent = or exceeds polys per cent		Below 10 per cent

RETICULOCYTES: Lack of Effect of Liver Treatment on the Circulating Reticulocytes in the Pigeon, Heimann, H., Connery, J. E., and Goldwater, L. J. Am. J. M. Sc. 188: 343, 1934.

From these experiments the following conclusions seem warranted:

1. The percentage of the circulating reticulocytes in the blood of the pigeon is subject to wide fluctuations.

2. The various test substances used in this study, including the "incomplete" diet, had no significant effect upon the percentage of the circulating reticulocytes in the pigeon.

3. In the authors' hands this technic does not lend itself to the biologic assay of the potency of materials used in the macrocytic hyperchromic anemias.

BICHLORIDE POISONING, TREATMENT OF: Study of 46 Cases, Porter, W. B., and Simons, C. E. Am. J. M. Sc. 188: 375, 1934.

Treatment in Detail: 1. Immediate gastric lavage with a saturated solution of sodium bicarbonate, temperature 100° F. This is continued until the return fluid is clear. The lavage is repeated every twelve hours for the first five days and is continued over a longer period if the chemical analysis of the washings shows mercury.

2. Morphine sulphate is administered immediately after the primary gastric lavage. This is repeated at intervals dependent upon the degree of shock, vomiting and pain; but the principle should be to relieve discomfort, retching and shock.

3. Sodium bicarbonate, 500 c.c. of a 5 per cent solution, is given intravenously immediately after the lavage, and 1,000 c.c. of normal saline solution are administered subcutaneously. As long as vomiting persists the same amount of each solution is repeated every twelve hours.

4. Sodium bicarbonate 5 gm. is given orally every three hours during the day and every four hours during the night. The amount of bicarbonate may be varied provided the urine is kept alkaline to litmus.

5. The total daily fluid intake must be at least 5,000 c.c. for an adult, and this amount must be maintained by oral, subcutaneous, or intravenous route, dependent upon the ability of the patient to retain the substances taken orally. Preference is always given the oral method.

6. The daily diet is orange juice 500 c.c., milk 1,000 c.c. and beta lactose 100 gm. One egg daily is added as soon as vomiting is controlled. The feedings should be given every three hours. If vomiting interrupts the feeding schedule, 10 per cent glucose solution is given intravenously in amounts sufficient to maintain an intake of at least 1,000 calories. The bicarbonate solution can be made with the glucose solution and the injection given by the intravenous "drip" method. After the first week adequate nutrition and medication are in some cases interrupted by the development of a severe stomatitis and esophagitis. In two of the patients of this series a gastrostomy was done and we feel that it was the deciding factor in recovery. All the food and medicine were given through the gastrostomy tube and only water was given orally.

7. A colonic irrigation, using 5 per cent sodium bicarbonate solution, is given daily and is continued until recovery is assured.

While there is no known specific antidote for corrosive sublimate poisoning, yet a therapeutic scheme which emphasizes the use of sodium bicarbonate solution for gastric lavage, for colonic irrigation, and for dosage in amounts sufficient to maintain urine alkaline to litmus apparently reduced the mortality and morbidity in this series of patients so treated.

A concept of the mechanism of renal insufficiency in mercury nephrosis is presented and a tenable explanation of the mode of action of alkalinization in preventing uremia is offered.

ENCEPHALITIS, Acute, Pathologic Changes of the St. Louis Type, McCordock, H. A., Collier, W., and Gray, S. H.: J. A. M. A. 103: 822, 1934.

The severe cases of the St. Louis type differed from the lethargic type in the following respects:

1. The meninges showed more intense infiltration with mononuclear cells than usually was found in the lethargic type.

2. Degenerative changes in the nerve cells were more frequent and neuronophagia was more marked.

3. The inflammatory foci were more widespread throughout the brain, often occurring in great numbers in the cerebral cortex, and were not restricted to the midbrain or basal nuclei.

4. The cranial nerve nuclei, especially the third, rarely showed degenerative changes such as are frequent in the von Economo type.

5. There was more extensive involvement of the spinal cord in the St. Louis type.

As the epidemic progressed, the lesions became less intense and not so widely scattered. Many of the milder cases showed about the same degree and intensity and a similar distribution in the midbrain, basal nuclei and pons as was seen in the lethargic type. Therefore, as far as these milder cases are concerned it is impossible to differentiate them with any degree of certainty from the lethargic type on the basis of the pathologic lesions alone.

The lesions described by the Japanese in their type *B. encephalitis* are similar in many respects to those of the St. Louis type. The intensity of the meningeal infiltration, the frequency and distribution of the focal collections of cells, the absence of cranial nerve nuclei involvement, and the frequent presence of lesions in the spinal cord, are strikingly similar in both of these types. The areas of softening (associated with the disease) and the retrogressive changes in the cellular foci (glial nodules) which they described were infrequent in our material.

The essential pathologic process in the St. Louis type of encephalitis is a nonsuppurative inflammation of the nervous system characterized by intense vascular congestion, cellular infiltration, and degenerative changes in the nerve cells.

Severe examples of the disease which closely resemble the Japanese type B^2 can readily be distinguished from the lethargic type, although the milder cases cannot be differentiated from the latter on the basis of the pathologic lesions alone.

TYPHOID: H and O Agglutination of B. typhosus in a Group of Suspected Typhoid Cases and in a Group of Unsuspected Individuals, Lewin, W. S. A. M. J. 8: 731, 1934.

In a series of 32 proved typhoid cases "H" agglutination in a serum dilution of 1 in 100 was positive in 81 per cent. In 62 nontyphoid cases only one showed "H" agglutination in a dilution of 1 in 100; the serum from this same case agglutinated *B. typhosus* 0 901 in dilutions up to 1 in 400, and there was a history of three weeks' illness, possibly typhoid, previous to admission to the hospital. Referring to the diagnostic titer for "H" agglutination in typhoid, Felix states: "In 'H' agglutination even a weak reaction in a serum dilution of 1 in 100, corresponding to + or ±, may be considered 'positive.'" The author's findings indicate that 1 in 100 is a satisfactory diagnostic titer for "H" agglutination in typhoid fever, provided the clinical signs and symptoms and the past history of the patient are considered.

The higher percentage of "O" agglutination results in typhoid cases with negative blood cultures as compared with those cases with positive blood cultures tends to confirm the opinion formed by some observers that "O" agglutination in high titer is a good prognostic sign.

The results of the tests indicate that, while 1 in 500 as a diagnostic "O" titer, as suggested by Dulaney, is too high, that of 1 in 100, as recommended by Felix, is too low. Lewin considers that a strong (+++) "O" agglutination in a serum dilution of 1 in 200 is a more acceptable minimum diagnostic titer.

The results obtained with the strains *B. typhosus* "H" and "O" have proved of greater diagnostic value than the polyvalent saline suspension. Emerging from this investigation, agglutination of the "H" strain to a titer of 1 in 100, and the "O" to a titer of not less than 1 in 200, is suggested as acceptable diagnostic titers. In the case of initial negative results, the test should be repeated with a specimen of serum collected at a later date.

"H" and "O" agglutination results in suspected typhoid cases must be considered together with the past history of the patient.

TUBERCLE BACILLI, New Medium for Rapid Cultivation of, Guernon, A. Am. Rev. Tubere. 30: 510, 1934.

The medium suggested is prepared as follows:

Agar 0.86 per cent; same amount of peptone; 1.73 per cent potato meal; 3.48 per cent glycerin and 26.09 egg, with the addition of gentian violet 1-30,000 put up in tubes, as a more convenient method.

1. Dissolve, as completely as possible, by stirring with a glass rod, 10 gm. of potato meal and 5 gm. of peptone in a beaker containing 385 c.c. of distilled water.
2. Add 5 gm. of agar, and heat mixture to boiling point, till agar is completely dissolved.
3. Cool to 65° C., then add a mixture containing 20 c.c. of glycerin, 150 c.c. egg and 1.8 c.c. of a 1 per cent alcoholic solution of gentian violet (previously filtered).
4. Filter mixture.
5. Tube in quantities of 7 or 8 c.c. and slant.
6. Inspissate for two hours at 70° C. on the first day and one hour on second day.

As contamination occurred only during the inoculation of the tubes, the medium was not tested for sterility.

Technic: Fresh sputum, containing varying numbers of bacilli, was treated according to Petroff's (1915) method: 4 per cent sodium hydroxide incubated, centrifugated and an addition of 7 drops of normal hydrochloric acid to every cubic centimeter of the mixture, again centrifugated for fifteen minutes and the sediment planted, a single loop on the surface of the medium. Ordinary corks were used, sealed with paraffin and incubated, sloping surface down. The last step is important in order to prevent excessive moisture.